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Bibliography (1) Hewitt, W. L., and Williams, Jr., B.: New England J. Med. *242*:119, 1950. (2) Recinos, Jr., A.; Ross, S.; Olshaker, B., and Twible, E.: New England J. Med. *241*:733, 1949. (3) Wood, E. J.: Lancet *2*:55, 1949.

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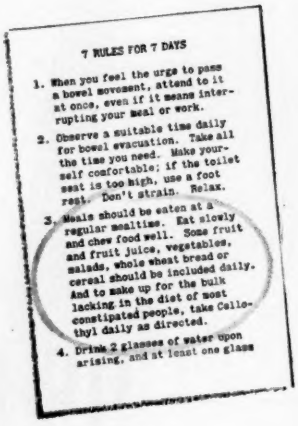

7 RULES FOR 7 DAYS

1. When you feel the urge to pass a bowel movement, attend to it at once, even if it means interrupting your meal or work.
2. Observe a suitable time daily for bowel evacuation. Take all the time you need. Make yourself comfortable; if the toilet seat is too high, use a foot rest. Don't strain. Relax.
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1. Bargen, J. A.: Gastroenterology *13*:275, 1949.
2. Musick, V. H.: J. Oklahoma M. A. *43*:360, 1950.
3. Schweig, K.: New York State J. Med. *48*:1822, 1948.
4. Council on Pharmacy and Chemistry: J.A.M.A. *143*:897, 1950.

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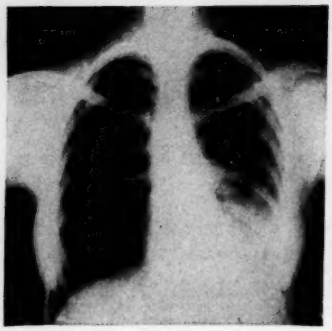

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CONTENTS

PAGE

The Erythrocyte Coproporphyrin: Variation in Respect to Erythrocyte Protoporphyrin and Reticulocytes in Certain of the Anemias. C. J. WATSON, M.D., WITH THE TECHNICAL ASSISTANCE OF MISS V. E. HAWKINSON, MISS IRENE BOSSENMAIER AND MRS. RITA HUGHES, MINNEAPOLIS 797

Prophylaxis of Motion Sickness: Evaluation of Some Drugs in Seasickness. MAJOR HERMAN I. CHINN, MEDICAL SERVICE CORPS, UNITED STATES AIR FORCE; WERNER K. NOELL, M.D., RANDOLPH FIELD, TEXAS, AND LIEUTENANT COLONEL PAUL K. SMITH, UNITED STATES AIR FORCE, AND LIEUTENANT COLONEL PAUL K. SMITH, UNITED STATES AIR FORCE. 810

Pheochromocytoma and Essential Hypertensive Vascular Disease. MARCEL GOLDENBERG, M.D.; HENRY ARANOW JR., M.D.; ALFRED A. SMITH, M.S., AND MOGENS FABER, M.D., NEW YORK 823

Current Concepts of Malaria, with a Review of Five Hundred and Ten Admissions to a Veterans Hospital. ROBERT SCHWARTZ, M.D.; MATTHEW M. MANSUY, M.D., AND WINFIELD C. JOHN, M.D., ASPINWALL, PA. 837

Alterations in Renal Function, Including Hematuria, in Man During Intracranial Air Studies: Alterations in Cardiac Function. S. J. WEINBERG, M.D.; J. R. GOODMAN, PH.D., AND M. C. BUSHARD, M.D., LOS ANGELES 857

Studies of Immunologic Reactions of Patients with Hodgkin's Disease: Antibody Reaction to Typhoid Immunization. GEORGE T. HOFFMANN, M.D., AND ANTONIO ROTTINO, M.D., NEW YORK 872

Gangrene of the Extremities: A Recently Recognized Complication of Severe Meningococcic Infection. H. A. WEINER, M.D., STATEN ISLAND, N. Y. 877

Progress Notes on Fifty Diabetic Patients Followed Twenty-Five or More Years. RUTH E. REUTING, M.D., BOSTON 891

Action of Atropine on the Cardiovascular System in Normal Persons. L. A. NALEFSKI, M.D., AND C. F. G. BROWN, M.D., CHICAGO 898

Liver Dysfunction Following Abdominal Operations: The Significance of Postoperative Hyperbilirubinemia. WILLIAM GELLER, M.D., AND HENRY J. TAGNON, M.D., NEW YORK 908

Studies on the Effects of Parenteral Quinidine Administration. HARRIS BLINDER, M.D.; JULIUS BURSTEIN, M.D.; WILLIAM HOROWITZ, M.D.; EUGENE GERSH, M.D., AND RAANAN SMELIN, M.D., NEW YORK 917

PROGRESS IN INTERNAL MEDICINE:

Annual Review of Rheumatic Diseases. HANS WAINE, M.D., BOSTON 934

BOOK REVIEWS 970

CONTENTS OF VOLUME 86 i

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and for the reporting of research and observation in the domain of internal medicine.

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THE ERYTHROCYTE COPROPORPHYRIN

Variation in Respect to Erythrocyte Protoporphyrin and Reticulocytes in Certain of the Anemias

C. J. WATSON, M.D.

With the Technical Assistance of Miss V. E. Hawkinson, Miss Irene Bossenmaier and Mrs. Rita Hughes

MINNEAPOLIS

THE PRESENCE of free protoporphyrin in the circulating red blood cells was first described in 1928 by van den Bergh and Hyman.[1] This discovery was widely confirmed, and in the intervening period considerable knowledge has been gained of variations in concentration in disease.[2] In 1936 it was pointed out that reticulocytes are especially rich in porphyrin.[3] At that time a satisfactory method of quantitative determination was not available. Later, with the use of the method devised in collaboration with Grinstein,[4] it soon became apparent that the correlation of erythrocyte porphyrin concentration with reticulocyte percentage varied considerably with the situation at hand.[2a] In acute phenylhydrazine anemia of rabbits the correlation was quite close; in pernicious anemia with liver therapy the peak of porphyrin concentration in the red cells was considerably later than the peak of

From the Department of Medicine, University of Minnesota Hospital.

This study was aided by a grant (RG 345) from the Division of Research Grants and Fellowships, United States Public Health Service, and from the Medical Research Fund of the Graduate School, University of Minnesota.

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reticulocyte percentage; in iron deficiency anemias and lead poisoning very great increases in porphyrin were often observed with relatively low reticulocyte percentage, and finally, in hemolytic anemias the porphyrin value was usually but moderately increased in the face of high reticulocyte counts. In these earlier studies coproporphyrin was sought (on the basis of chloroform insolubility) on a number of occasions, but it was not observed.[2a, b] In retrospect, it is believed that this failure was due (1) to selection of samples having great increases of EP (erythrocyte protoporphyrin) and very small amounts of ECP (erythrocyte coproporphyrin), as in iron deficiency anemia, or of samples with normal or decreased amounts of EP and no ECP (see below), as in pernicious anemia in relapse; (2) to lack of a sufficiently sensitive fluorophotometer, and (3) to removal and loss of significant amounts of coproporphyrin by washing the ether or ethyl acetate extracts with distilled water. Schwartz and co-workers have recently discovered that coproporphyrin is usually present in erythrocytes in addition to protoporphyrin.[5] Studying experimental anemias in rabbits and dogs, Schwartz and Wikoff [5] have shown that the concentration of ECP is much more closely correlated with the reticulocyte percentage than that of EP. Furthermore, Schwartz has succeeded in crystallizing coproporphyrin from the erythrocytes of these animals and has identified the crystals as type III isomer [5b]; in other words, it has the same configuration as the hemoglobin protoporphyrin and, therefore, is quite probably related to hemoglobin synthesis, a matter to be considered again in the following paragraphs. It may be noted that, while coproporphyrin III was thus clearly the preponderant coproporphyrin isomer in these erythrocytes, the fluorescence-quenching technic of isomer analysis [6] has also indicated the presence of small but significant amounts of type I isomer.[5]

PRESENT STUDIES

We have been engaged for some time in studying the ECP concentration in normal human subjects and in persons with various anemias. The method employed is to be described elsewhere.[5b] It will suffice to say now that the method depends on the chloroform solubility of protoporphyrin as contrasted with the insolubility of coproporphyrin,

5. (*a*) Schwartz, S.: Glickman, M.; Hunter, R., and Wallace, J.: Studies of Porphyrin Metabolism: III. The Relation of Erythropoiesis to the Excretion of Coproporphyrin by Dogs and Rabbits, and to the Concentration of Coproporphyrin and Protoporphyrin in Rabbit Erythrocytes, Argonne National Laboratory Report Ch. 3720, written for the United States Atomic Energy Commission, Argonne National Laboratory, Chicago, 1947. (*b*) Schwartz, S., and Wikoff, H.: Erythrocyte Porphyrins, to be published.

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and on the much lower "HCl number" of the latter porphyrin, in other words, the ease with which it is extracted from ether with very dilute hydrochloric acid. The striking difference in this respect is shown in figure 1. The data also serve as further evidence of the presence of coproporphyrin. The data for the normal group of persons are given in table 1. The results of statistical study of the data in table 1 are given in table 2. A significant correlation, $r = -0.78$, was found between hemoglobin (Hb.) and EP for the entire group ($\delta + \varphi$). It is noted that of the 50 persons comprising the group, 20 had values of 0 for the ECP. In this connection it should be emphasized that 5 to 7 cc. of packed cells

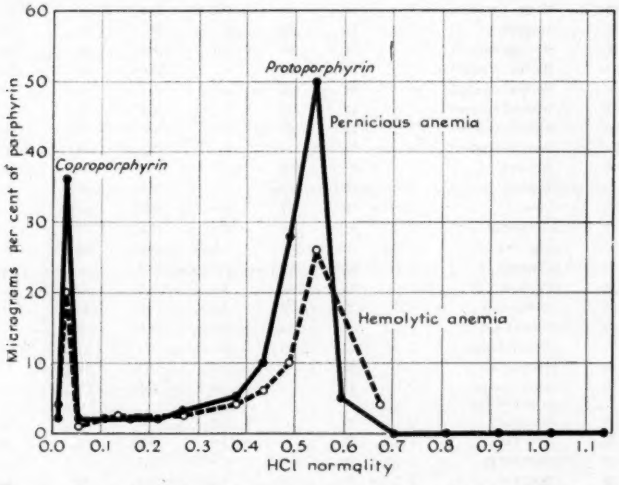

Fig. 1.—Extraction of erythrocyte coproporphyrin and protoporphyrin from ether by hydrochloric acid of varying concentration.

was used, and it is quite possible that small amounts of ECP might have been determined had larger volumes of red cells been employed. The same reservation must be made for the data on the group with pernicious anemia (relapse), which will be given in the following material.

It may also be observed in table 1 that ECP exceeded 1.0 microgram per 100 cc. of erythrocytes in but three subjects, nos. 28, 30 and 43. Since all three were women with a relatively low hemoglobin level and relatively high EP content, it seems not unlikely, in view of the significant differences noted in table 2 and the correlation between reduced hemoglobin and increased EP values, that a slight degree of iron deficiency was present. It is noted, however, that in certain other subjects, nos. 32 and 47, relatively low hemoglobin levels were encoun-

TABLE 1.—*Erythrocyte Porphyrins in Normal Persons*

Subject No.	Occupation	Sex	Age	EP, Micrograms/100 Cc.	ECP, Micrograms/100 Cc.	Hb., Gm./100 Cc.	Hematocrit, %	Reticulocytes, %
1	Physician	♂	28	27	0.7	15.1	46	0.5
2	Physician	♂	28	30	0	15.7	48.5	0.4
3	Physician	♂	26	24	0.6	15.0	44.6	0.6
4	Physician	♂	29	30	0.4	15.2	44.5	0.5
5	Physician	♂	26	28	0.6	15.0	46	0.8
6	Physician	♂	29	30	0	14.8	46	0.5
7	Physician	♂	32	42	1.0	16.3	48.5	1.0
8	Physician	♂	27	24	0.5	17.0	48	0.7
9	Medical student	♂	17	35	1.0	13.2	43.5	1.0
10	Medical student	♂	24	25	0	15.0	45	0.5
11	Chemist	♂	27	28	0	16.4	47	0.4
12	Medical student	♂	24	28	1.0	16.4	48	1.2
13	Medical student	♂	23	27	0	15.0	45	0.6
14	Medical student	♂	25	35	0.5	13.5	43.5	0.6
15	Medical student	♂	24	27	0	15.5	46	0.5
16	Medical student	♂	22	26	0	15.6	46.5	0.6
17	Medical student	♂	22	25	0	15.8	47	0.4
18	Student	♂	31	25	0	15.2	46	0.5
19	Student	♂	33	24	0	15.8	47.2	0.6
20	Clerk	♂	25	29	0	15.8	46.2	0.6
21	Technician	♀	26	40	0	13.5	43	0.6
22	Chemist	♀	26	37	0.4	13.9	42	0.8
23	Chemist	♀	24	32	0	13.2	40	0.8
24	Chemist	♀	25	42	1.0	14.2	37.5	0.9
25	Technician	♀	23	50	1.0	12.6	38.0	1.5
26	Technician	♀	24	34	0	14.0	39.5	0.5
27	Technician	♀	26	33	0	13.4	....	0.5
28	Technician	♀	29	52	1.2	11.7	38.2	1.5
29	Laboratory attendant	♀	21	38	1.0	13.1	40.5	1.1
30	Secretary	♀	22	50	2.0	12.5	40	1.1
31	Secretary	♀	26	41	1.0	12.8	39.5	0.9
32	Secretary	♀	18	45	1.0	11.7	....	1.0
33	Secretary	♀	22	35	1.0	13.0	42	1.0
34	Nurse	♀	27	45	1.0	13.6	41.5	1.1
35	Nurse	♀	23	37	0	15.1	46.2	0.4
36	Nurse	♀	22	47	1.0	12.0	37.0	1.2
37	Nurse	♀	25	42	0.5	14.5	43	0.6
38	Nurse	♀	24	46	1.0	13.2	39.5	1.1
39	Instructor	♀	40	36	0.5	13.5	40	0.8
40	Instructor	♀	70	35	0	15.0	45	0.5
41	Nurse	♀	25	40	0.5	13.0	39.2	0.5
42	Technician	♀	22	45	0	14.0	41	0.6
43	Nurse	♀	19	52	2.0	12.0	38.5	1.4
44	Nurse	♀	29	40	1.0	13.6	42	0.9
45	Nurse	♀	26	48	1.0	12.9	38	1.2
46	Nurse	♀	27	44	0	13.5	42	0.5
47	Nurse	♀	20	49	1.0	12.0	36.2	1.3
48	Nurse	♀	24	40	0	14.0	43	0.6
49	Chemist	♀	23	34	0	13.9	43.2	0.6
50	Student	♀	22	42	0.6	13.0	42	0.7

TABLE 2.—*Statistical Data for Values Given in Table 1*

	EP, Micrograms/ 100 Cc.	ECP, Micrograms/ 100 Cc.	Hb., Gm./ 100 Cc.	Hematocrit, %	Reticulocytes, %
Range for entire group.....	24 to 52	0 to 2.0	11.7 to 17.0	36.2 to 48.5	0.4 to 1.5
Mean	36.4	0.5	14.1	42.9	0.78
S. D.	8.5	0.54	1.36	3.5	0.31
Mean for ♂.....	28.5	0.3	15.4	46.2	0.6
S. D. for ♂.....	4.5	0.39	0.90	1.5	0.22
Mean for ♀.....	41.7	0.7	13.3	40.6	0.9
S. D. for ♀.....	5.9	0.6	0.89	2.4	0.32
t for significance of differences between ♂ and ♀	8.52*	2.31†	8.06*	9.04*	3.0†

* Highly significant.
† Significant.

TABLE 3.—*Representative Data for Erythrocyte Porphyrins in Certain Anemias*

Patient	Type of Anemia	Hb., Gm./ 100 Cc.	Reticulocytes, %	EP, Micrograms per 100 Cc.	ECP, Micrograms per 100 Cc.
	Normal range.....	....	....	20 to 40	0 to 1.0
E. E.	Pernicious	10.0	0.5	30	0
H. E.	Pernicious	8.8	0.8	40	0
J. J.	Pernicious	5.2	0.4	26	0
J. W.	Pernicious	10.2	0.5	34	0
L. G.	Iron deficiency	10.4	4.2	390	5.0
E. T.	Iron deficiency	10.0	1.2	330	2.0
E. A.	Iron deficiency	6.5	1.1	310	1.8
L. H.	Iron deficiency	5.0	1.3	180	1.0
F. G.	Hemolytic	9.5	12.2	65	32.5
M. B.	Hemolytic	10.7	22.5	60	35.0
J. D.	Hemolytic	10.5* 14.6†	30.5* 4.5†	120* 148†	52.0* 5.0†
H. G.	Hemolytic	10.1	12.8	62	30.0

* Before splenectomy.
† After splenectomy.

TABLE 4.—*Erythrocyte Porphyrins in Lead Poisoning*

Patient	Hb., Gm./ 100 Cc.	Reticulocytes, %	EP, Micrograms/ 100 Cc.	ECP, Micrograms/ 100 Cc.	UCP,* Micrograms/ 24 Hr.
L. S.	15.0	4.4	452	6	190
E. R.	12.8	4.2	1,300	20	721
V. L.	5.7	3.5	211	58	1,480
B. L.	12.3	2.9	400	1.5	4,000

* Urinary coproporphyrins.

tered without increase of ECP above 1.0 microgram. The values for EP are slightly higher than those previously recorded from this laboratory.[2a, b] Meanwhile, considerably higher values for certain presumably normal persons have been reported by others.[7] The reason for this is not clear, but it is evident that latent abnormality, such as iron deficiency or chemical toxicity, could easily produce misleading elevations. On the basis of our present and previous data, it is believed that values

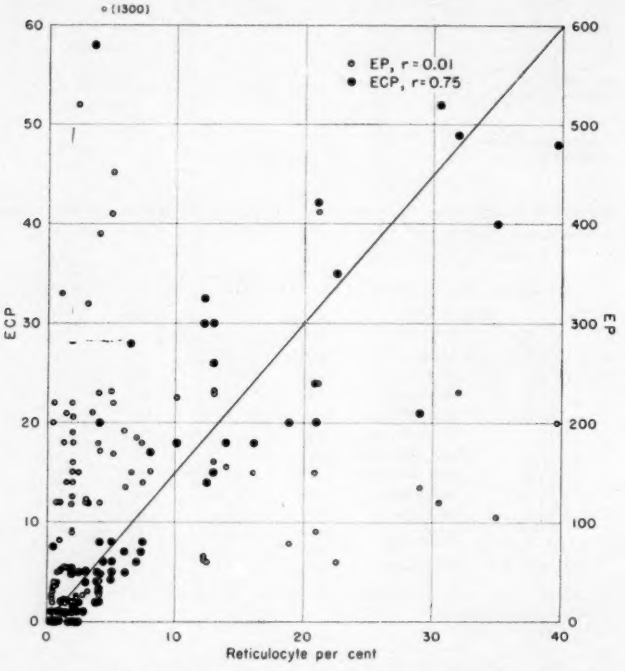

Fig. 2.—EP and ECP values in relation to reticulocyte percentage.

above 60 micrograms per 100 cc. are probably abnormal, whether the person has any symptoms or not.

The present study has revealed rather characteristic patterns of the erythrocyte porphyrins in the common anemias. Representative data are given in table 3. It is seen that the EP is low and the ECP not demonstrable in pernicious anemia in relapse. In iron deficiency anemias

7. Cartwright and others.[2c] Ward, E., and Mason, H. L.: Free Erythrocyte Protoporphyrin, J. Clin. Investigation **29**:905, 1950.

the EP is disproportionately increased; in hemolytic anemias, conversely, the ECP is disproportionately increased. In lead poisoning it is evident that a more complex situation exists, though we have been able to study but four human cases since the ECP was discovered. The data for these are given in table 4. These limited observations suggest that the severer the anemia, presumably the more serious the abnormality of the bone marrow, and the greater the increase of

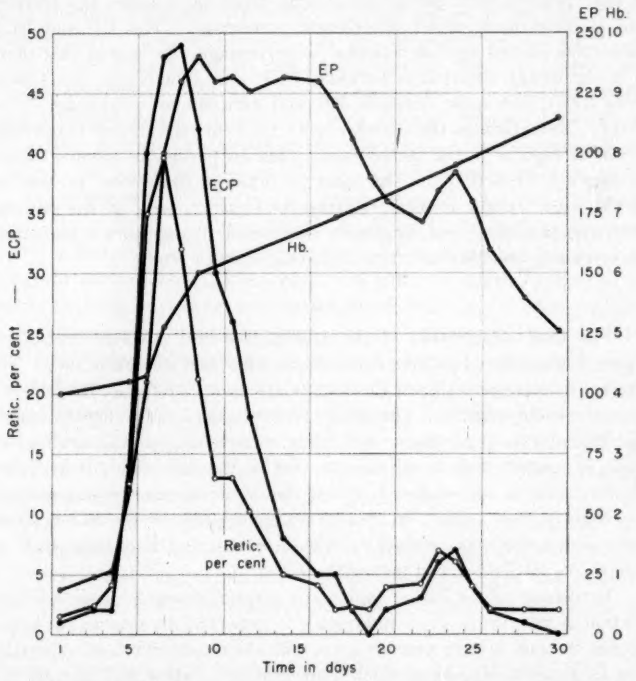

Fig. 3.—EP and ECP values in relation to hemoglobin concentration and reticulocyte percentage in C. O., a woman 49 years of age who had pernicious anemia treated with crystalline vitamin B_{12}. The latter was given in the amount of 15 mg. three times weekly, commencing on day 3. On day 18, 200 mg. of iron, as saccharated iron oxide, was given intravenously. (This material was obtained through the courtesy of Sharp and Dohme, Inc., Glenolden, Pa.)

ECP. It is of interest, however, that there is no apparent correlation of the ECP with the increase of coproporphyrin III in the urine. As will be noted in the following paragraphs, however, it may well be related to the coproporphyrin of developing red cells in the bone marrow.

With the exception of lead poisoning and the metabolic error, porphyria, in which ECP and EUP (erythrocyte uroporphyrin) may be increased without any increase in reticulocytes, it is evident that a much closer correlation exists between ECP and reticulocyte percentage than between EP and reticulocyte percentage. Figure 2 shows the results of 86 determinations in 43 patients with various types of disease, for the most part patients with anemia. The data include 45 determinations in four persons with pernicious anemia receiving vitamin B_{12} therapy and at different levels of reticulocyte percentage. The EP and ECP values are plotted against reticulocyte percentage. It is seen that there is a significant correlation between ECP and reticulocyte percentage ($r = 0.75$), but none between EP and reticulocyte percentage ($r = 0.01$). Nevertheless, the correlation of ECP to reticulocyte percentage is not as high as in the homogeneous data on pernicious anemia shown in figure 3 ($r = 0.94$). The most pronounced deviations, accounting in the main for the lower correlation in figure 2, were in the patients with lead poisoning, and, as already mentioned, this appears to constitute an especially complex situation requiring further study.

COMMENT

The time relationship of the reticulocyte and porphyrin peaks in figure 3 are believed to have considerable fundamental significance. The previously recognized lag of EP with relation to the reticulocyte peak [2a, b] is again quite evident. The ECP, however, lags only slightly behind the reticulocyte percentage, and, after vitamin B_{12} administration, its peak is reached well in advance of that of the EP. This relationship is seen again in the smaller response due to intravenously administered saccharated iron oxide. In this instance the peak for the two erythrocyte porphyrins was reached on the same day, but it is clear that the rise of the ECP preceded that of the EP.

Returning to the earlier and much greater increases, after administration of vitamin B_{12}, it is interesting to note that the gradient of hemoglobin increase is steep in association with the reticulocyte and, especially, the ECP peaks, becoming much more gradual as these fall, in spite of a sustained increase of the EP. These observations, together with the much more significant correlation of ECP and reticulocyte percentage and the erythrocyte porphyrin pattern in various anemias (table 3), suggest that the ECP is actually a sensitive index of the rate of hemoglobin synthesis (or attempted synthesis) in the bone marrow and are in accord with the view that ECP is a normal precursor of the hemoglobin protoporphyrin.[8] This concept, which involves decarboxylation and dehydro-

8. Grinstein, M.; Kamen, M. D.; Wikoff, H. M., and Moore, C. V.: Isotopic Studies of Porphyrin and Hemoglobin Metabolism, J. Biol. Chem. **182**:715, 1950. Since this was written, Neuberger and others (*Nature, London* **165**:948, 1950) have offered a hypothesis of porphyrin biosynthesis which includes this relationship.

genation (removal of two formic acid molecules), is quite the opposite of that initially proposed by van den Bergh,[9] who believed that protoporphyrin was converted to coproporphyrin in the liver and that the urinary and biliary coproporphyrin was thus derived. Evidence against such a conversion was reported from this laboratory a number of years ago.[10]

The present data may be considered briefly with respect to the concept that coproporphyrin III is the normal precursor of the hemoglobin protoporphyrin, also with respect to the hypothesis of Lemberg and Legge,[11] according to which one of the specific dipyrrylmethene precursors necessary to the formation of coproporphyrin III is normally decarboxylated and, on condensing with another (dipropionic) dipyrrylmethene molecule, gives rise to protoporphyrin. Lemberg and Legge believed this would explain the lack of appearance of more than traces of coproporphyrin III in normal circumstances. The present study reveals, however, that coproporphyrin is present in the erythrocytes even normally and that its concentration increases to a marked degree with increased erythropoiesis, even when the latter is relatively normal in character, as in hemolytic anemias, in pernicious anemia after vitamin B_{12} therapy or after blood loss. Experimental studies of the bone marrow and erythrocyte porphyrins, which are reported separately,[12] have revealed that the developing erythrocytes in the bone marrow of rabbits in lead poisoning, and even more significantly after blood loss, contain relatively large amounts of coproporphyrin which diminish to a striking degree as the cells mature and leave the bone marrow. These findings, together with those now described, are in harmony with the first-mentioned concept, i. e., that coproporphyrin III is normally intermediary in hemoglobin synthesis. They do not, however, exclude the hypothesis of Lemberg and Legge, and it is possible that still other explanations may be found. To harmonize the present observations with the Lemberg-

9. van den Bergh, A. A. H.; Grotepass, W., and Revers, F. E.: Beitrag über das Porphyrin in Blut und Galle, Klin. Wchnschr. **11**:1534, 1932.

10. Watson, C. J.; Pass, I. J., and Schwartz, S.: A Study of the Supposed Conversion of Protoporphyrin to Coproporphyrin by the Liver: I. The Fate of Parenterally Administered Protoporphyrin in Dogs with Bile Renal Fistulae, J. Biol. Chem. **139**:583, 1941. Salzburg, P., and Watson, C. J.: A Study of the Supposed Conversion of Protoporphyrin to Coproporphyrin by the Liver: II. The Porphyrin Metabolism of Rabbit Liver, ibid. **139**:593, 1941.

11. Lemberg, R., and Legge, J. W.: Hematin Compounds and Bile Pigments, New York, Interscience Publishers, Inc., 1949.

12. Schmid, R.; Schwartz, S., and Watson, C. J.: The Relationship of Copro- and Protoporphyrin in the Bone Marrow and Circulating Erythrocytes in Experimental Anemias, to be published.

Legge concept, it would be necessary to assume that, with a heightened production of precursors (the specific dipyrrylmethenes postulated), the side formation of coproporphyrin III would increase proportionately, possibly as a manifestation of compensation in excess. This explanation would appear to be logical for lead poisoning, in which the excessive type III coproporphyrinuria could then be related simply to an accentuation of this side formation by virtue of an enzymatic interference (see below). This would imply, however, that one might also anticipate at least moderate increases of this isomer in the urine in posthemorrhagic or hemolytic anemias, but these have not been observed. This, in fact, favors a direct relationship of coproporphyrin to protoporphyrin, rather than the Lemberg-Legge hypothesis. Such an intermediary role of coproporphyrin III accords well with the present findings in various anemias. Thus, in pernicious anemia in relapse, hemoglobin synthesis is greatly retarded, owing to the megaloblastic state of the bone marrow, and it is not surprising that the EP is relatively small and the ECP not demonstrable. In an ordinary hemolytic anemia, on the contrary, erythropoiesis and hemoglobin synthesis proceed in normal fashion, but at an unusually rapid rate. Young erythrocytes are released from the bone marrow before completion of hemoglobin synthesis; hence, one might anticipate relatively large amounts of as yet unconverted coproporphyrin. Since there is no lack of iron, most of the protoporphyrin formed is complexed, and only moderate increases of free protoporphyrin are observed. By way of contrast, the relatively great increase of EP and the slight or negible increase oi ECP in an iron deficiency anemia are logically construed as the expression of a much less rapid hemoglobin synthesis which allows more time for conversion of coproporphyrin to protoporphyrin, the latter then accumulating in the red cell because of the lack of iron.

The findings in lead poisoning may also be reconciled with this concept on the basis of partial enzymatic interference. Rimington [13] earlier proposed that lead blocked the enzymatic formation of heme from protoporphyrin and iron and that coproporphyrin III formation was the result of this disturbance. According to the concept of a direct relationship of coproporphyrin III with protoporphyrin, the lead simply interferes with a paired decarboxylase-dehydrogenase system which functions in converting coproporphyrin (III) to protoporphyrin. Kench [14] previously objected to Rimington's enzymatic theory on the ground that the degree of anemia, or total deficit of hemoglobin in many cases of plumb-

13. Rimington, C.: An Enzymic Theory of Haemopoiesis, Compt. rend. d. trav. du lab. Carlsberg, série chim. **22**:454, 1938.

14. Kench, J. E.; Gillam, A. E., and Lane, R. E.: Haemopoiesis in Lead Poisoning, Biochem. J. **36**:384, 1942.

ism, is out of all proportion to the relatively small amounts of free porphyrins which are in evidence. It is entirely possible, however, that lead also acts at a lower level in the pathway of hemoglobin synthesis, i. e., in partially preventing the synthesis of coproporphyrin III. This would assume a disturbance as well of the enzyme system essential to this synthesis. Assumptions of enzyme interference by lead are quite in accord with general knowledge of the effect of heavy metals on cellular enzyme systems. In figure 4 an attempt is made to show the possible relationships entailed in such a concept. According to this, the precursors of coproporphyrin ought to be demonstrable in increased amounts either in the developing erythrocytes of the bone marrow or quite possibly in the circulating erythrocytes, if proper technics could be employed. In figure 4 it has also been indicated in accord with

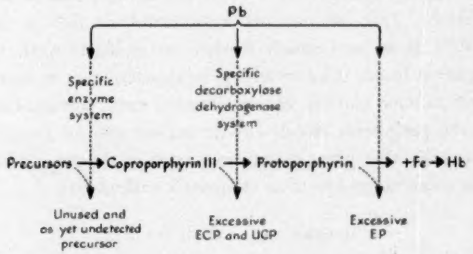

Fig. 4.—A suggestion concerning possible disturbances of porphyrin metabolism in lead poisoning.

Rimington's earlier view, that the lead disturbs the complexing of protoporphyrin with iron. This appears to be the most logical way of explaining the notable increases in EP which are a regular accompaniment of plumbism. It is not believed, however, that this protoporphyrin is then converted to coproporphyrin and excreted. The derivation of the excessive type III coproporphyrin in the urine in lead poisoning is probably not from ECP in any considerable part, as it is clear in table 3 that there may be large amounts in the urine with but minor increases in the circulating red cells. It is evident from the recent studies in rabbits,[12] however, that there is a striking decrease of coproporphyrin in the erythrocytes as they mature and leave the bone marrow to be excreted in the urine. It appears less likely that this decrease is due to destruction of developing red cells in the marrow than to liberation from intact cells, as an enormous number would have to be destroyed to supply the amounts of coproporphyrin found in the urine.

In this connection one need not assume that excessive urinary coproporphyrin III always originates from the bone marrow, or that it is necessarily derived from a disturbed hemoglobin synthesis. Derivation from the central nervous system in poliomyelitis,[15] or from the liver in "alcoholic" cirrhosis,[16] appears to be a reasonable possibility.

Some attention needs to be given to the possibility that the ECP is related to circulating normoblasts rather than to non-nucleated erythrocytes. In the aforementioned experiments of Schmid and his associates [12] the normoblasts of the bone marrow obviously contained relatively large amounts of coproporphyrin, and, when the ECP values were high as in phenylhydrazine anemia, normoblasts were readily found in the circulating blood. This question is receiving further study at present, and there is much reason to believe that non-nucleated erythrocytes also contain free coproporphyrin, as well as protoporphyrin, at least under many conditions. Thus, in patients with hemolytic anemia rather high values for ECP have been observed when normoblasts were not evident in the peripheral blood. Conversely, it is apparent that in some circumstances, such as bone marrow carcinomatosis, many normoblasts may be present in the peripheral blood without an increase of the ECP value. The latter implies that great differences exist in the rate of hemoglobin synthesis in some normoblasts as compared with others.

SUMMARY AND CONCLUSIONS

Human erythrocytes contain free coproporphyrin in addition to the protoporphyrin hitherto studied. In normal circumstances the amount does not exceed 2 micrograms per 100 cc. of red blood cells.

The amount of ECP (erythrocyte coproporphyrin) is significantly correlated with the reticulocyte percentage, especially in pernicious anemia during response to vitamin B_{12} therapy. The slight but consistent lag of the ECP in the latter situation, as well as the lack of strict correlation between ECP and reticulocytes at different levels, indicates that they represent sequential or closely related phenomena in the same fundamental process.

15. Watson, C. J.; Schulze, W.; Hawkinson, V., and Baker, A. B.: Coproporphyrinuria (Type III) in Acute Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **64**:73, 1947.

16. Watson, C. J.; Sutherland, D., and Hawkinson, V.: Studies of Coproporphyrin: V. The Isomer Distribution of per Diem Excretion of the Urinary Coproporphyrin in Cases of Cirrhosis of the Liver, J. Lab. & Clin. Med., to be published. Sutherland, D., and Watson, C. J.: Studies of Coproporphyrin: VI. The Effect of Alcohol on the per Diem Excretion and Isomer Distribution of the Urinary Coproporphyrins, ibid., to be published.

Characteristic patterns of EP (erythrocyte protoporphyrin) and ECP concentration have been observed in certain of the commoner anemias thus far studied. Pernicious anemia in relapse exhibits a low or normal EP and negligible or absent ECP, iron deficiency anemia a decided increase of EP, with slight or no rise of ECP, and the hemolytic anemias a relatively pronounced increase of ECP, with but moderate elevation of EP.

The observations on ECP indicate that this value is a rather sensitive chemical index of the rate of hemoglobin synthesis (or attempted synthesis) in the bone marrow.

PROPHYLAXIS OF MOTION SICKNESS

Evaluation of Some Drugs in Seasickness

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MOTION sickness represents a response to a particular pattern of vestibular discharges which are generated chiefly in the utriculus of the labyrinth and stimulate pathways through the cerebellum to the brain stem.[1] The response requires a lengthy process of summation since minutes to hours are needed until the vestibular discharges induce a variety of symptoms which culminate in vomiting. Conversely, a relatively rapid process of adaptation may suppress the manifestations of motion sickness. In addition, there are other ways of weakening or preventing the response. Thus, the effect of motion is minimized by assuming a supine position, which greatly reduces the stimulation of the

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1. Tyler, D. B., and Bard, P.: Motion Sickness, Physiol. Rev. **29**:311-369, 1949.

utriculus. Further, the reduction of psychological, visual, visceral or other facilitating influences may lower the incidence of motion sickness. Finally, there are certain drugs which are preventive.

During World War II extensive investigations centered on parasympatholytic agents, central nervous system stimulants or depressants, vitamins or mixtures of these compounds.[2] Of all these drugs only members of the atropine series were consistently of value in the prevention of motion sickness.[3] Of this group scopolamine (hyoscine) hydrobromide showed the greatest promise because of its effectiveness and its relatively low incidence of side effects.[2a] No compound or mixture investigated was shown superior to scopolamine alone.[2a]

The interesting possibility that a new series of drugs might be of value against motion sickness was suggested by the report that the antihistaminic agent dimenhydrinate (diphenhydramine 8-chlorotheophyllinate; dramamine®) prevented and "cured" seasickness in a high percentage of cases.[4] Although this report has been criticized because of the experimental design,[1] there seems little doubt that diphenhydramine does exert considerable protection. Both the 8-chlorotheophylline salt [5] and the hydrochloride [6] (benadryl®) have been shown to be approximately as effective as scopolamine in the prevention of airsickness.

The present experiment was designed with a threefold purpose: (1) to determine whether efficacy against motion sickness is related to antihistaminic action, (2) to compare a series of antihistaminic drugs with a known preventive of motion sickness and (3) to effect a rapid screening of potential preventives for subsequent testing in the airplane.

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2. (*a*) Smith, P. K.: Present Status of Drugs for Use in Motion Sickness with Particular Reference to Airsickness, Report no. 1, United States Air Force School of Aviation Medicine, Research Project no. 468, June 14, 1946. (*b*) Noble, R. L.: Treatment of Experimental Motion Sickness in Humans, Canad. J. Research **24**:10-20, 1946.

3. Holling, H. E.; McArdle, B., and Trotter, W. R.: Prevention of Seasickness by Drugs, Lancet **1**:127-129, 1944. Lilienthal, J. L.: The Effect of Hyoscine on Airsickness, J. Aviation Med. **16**:59-68, 1945. Tyler, D. B.: The Influence of a Placebo, Body Position and Medication on Motion Sickness, Am. J. Physiol. **146**: 458-466, 1946. Smith, P. K.: The Effectiveness of Some Motion Sickness Remedies in Preventing Air Sickness in Air Force Navigation Students, J. Aviation Med. **17**: 343-345, 1946.

4. Gay, L. N., and Carliner, P. E.: The Prevention and Treatment of Motion Sickness: I. Seasickness, Science **109**:359, 1949; Bull. Johns Hopkins Hosp. **84**:470-487, 1949.

5. Strickland, B. A., Jr., and Hahn, G. L.: The Effectiveness of Dramamine in the Prevention of Airsickness, Science **109**:359-360, 1949. Strickland, B. A.; Hahn, G. L., and Adler, H.: Studies on Airsickness, J. Aviation Med., to be published.

6. Chinn, H. I., and Oberst, F. W.: Effectiveness of Various Drugs in Prevention of Airsickness, Proc. Soc. Exper. Biol. & Med. **73**:218-219, 1950.

It was hoped that the study would yield some information on the basic aspects of the response pathway. Scopolamine hydrobromide was selected as the standard for comparison.

The effectiveness of certain drugs (atropine, scopolamine, diphenhydramine) against both motion sickness and parkinsonism suggests a common mechanism of action, possibly by anticholinergic means.[7] It seemed fruitful, therefore, to test certain antihistaminic agents which have been employed against parkinsonism, diphenhydramine salts (benadryl®[8] and dramamine®[9]) and phenindamine (thephorin®) tartrate,[10] as well as the promising antispasmodic, trihexyphenidyl (artane®).[11] Pyranisamine maleate (neo-antergan®) was studied because its strong antihistaminic action and low anticholinergic activity sharply differentiate it from the drugs just mentioned.[12] Chlorcyclizine (perazil®) hydrochloride was included because of the reported low incidence of side effects and long duration of action.[13]

EXPERIMENTAL STUDIES

The United States Army Transport General Maurice Rose was employed during its routine crossing from New York to Bremerhaven, Germany, and return. The General Rose is a 16,000 ton ship carrying as its full complement 1,042 troops and approximately 1,000 other passengers and crew. Troops were quartered in eight compartments of various sizes, all at the same level (on C deck). Male volunteers were employed as subjects and were in each of the compartments

7. Gair, D. S., and Ducey, J.: Chemical Structure of Substances Effective in Treatment of Parkinsonism, Arch. Int. Med. **85**:284-298 (Feb.) 1950.

8. Benadryl® (beta-dimethylaminoethylbenzhydryl ether hydrochloride) and placebos were supplied by Parke, Davis & Company, Detroit.

9. Dramamine® (beta-dimethylaminoethylbenzhydryl ether 8-chlorotheophyllinate) was supplied by G. D. Searle & Company, Chicago.

10. Thephorin® ([2-methyl-9-phenyl-2,3,4,9] tetrahydro-1-pyridindene hydrogen tartrate) was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

11. Artane® (3-[1-piperidyl]-1-phenyl-1-cyclohexyl-1-propanol hydrochloride) was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. Corbin, K. B.: Trihexyphenidyl: Evaluation of the New Agent in the Treatment of Parkinsonism, J. A. M. A. **141**:377-382 (Oct. 8) 1949. Doshay, L. J., and Constable, K.: Artane Therapy for Parkinsonism: A Preliminary Study of Results in 117 Cases, ibid. **140**:1317-1322 (Aug. 27) 1949.

12. Graham, J. D. P.: A Comparison of Some Antihistamine Substances, J. Pharmacol. & Exper. Therap. **91**:103-111, 1947. Neo-antergan® (N-[P-methoxybenzyl]-N^1, N^1-dimethyl-N-alpha-pyridyl-ethylenediamine maleate) was supplied by Merck & Company, Inc., Rahway, N. J.

13. Jaros, J. H.; Castillo, J. C., and de Beer, E. J.: The Clinical Application of a New Piperazine Compound: I. Human Pharmacology, Ann. Allergy **7**:458-465, 1949. Jaros, J. H.: The Clinical Application of a New Piperazine Compound: II. Clinical Observations, ibid. **7**:466-470, 1949. Perazil® (N-methyl-N^1-[4-chlorobenzhydryl] piperazine dihydrochloride) was supplied by Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

except the first at the extreme forward position of the ship. A questionnaire was completed before sailing to learn the subject's age, his susceptibility to various types of motion, flying experience and the like. Most of the men were less than 25 years of age, and approximately 80 per cent were under 30 years. There was no significant difference in age distribution among any of the experimental groups. The General Rose departed from New York Jan. 31, 1950 and arrived at Bremerhaven February 9, departing in turn February 12 and arriving in New York February 20.

Approximately half the men (47 per cent) on the outward trip were making their first ocean crossing, and 30 per cent of these had been seasick at least once. In the group given placebos only 20 per cent of the subjects had been sick before, whereas 35 to 37 per cent of those in the groups given scopolamine, dimenhydrinate and diphenhydramine hydrochloride had been seasick. Several subjects were discarded before completion of the experiment because of uncooperativeness, failure to take medicaments, administrative difficulties, etc. A total of 608 completed the test. The subjects were divided at random into seven groups for the prophylactic study. Every compartment had equal representation from each of these groups so that no spatial differentiation existed. The groups received, respectively, (1) placebo, (2) scopolamine hydrobromide, 0.75 mg., (3) dimenhydrinate, 100 mg., (4) diphenhydramine hydrochloride, 50 mg., (5) trihexyphenidyl, 2.5 mg., (6) pyranisamine maleate, 50 mg., and (7) phenindamine tartrate, 25 mg. All drugs were in capsules of identical size and appearance. The first capsule was given at 6:00 p. m., about three hours after sailing, but while the sea was still entirely smooth. Subsequent capsules were given at 6:00 and 11:00 a. m., before breakfast and lunch, respectively, and at 6:00 p. m., immediately after dinner. Medication was continued through the 6:00 a. m. distribution of the following day (a total of five capsules). All medicaments were swallowed immediately with water while the subjects were under observation. Each person then completed a detailed questionnaire to determine the incidence and time of vomiting or nausea, as well as any side effects which might be attributed to the drugs. So far as possible interviews confirmed and supplemented these data.

On the return trip from Bremerhaven to New York the decreased number of troops aboard ship allowed only five experimental groups. A total of 342 subjects completed the experiment. The main difference between these subjects and those used previously was their seagoing experience. Practically all the persons had made at least one ocean voyage, and 59 per cent had been seasick before. The distribution of these susceptibles among the various groups was uniform. The groups received, respectively, (1) placebo, (2) dimenhydrinate, 100 mg., (3) scopolamine hydrobromide, 0.75 mg., (4) trihexyphenidyl, 5 mg., and (5) chlorcyclizine hydrochloride, 50 mg. Placebo, dimenhydrinate and trihexyphenidyl capsules were distributed three times daily, as already described, while scopolamine and chlorcyclizine were given twice daily (morning and night). Placebos were given to the latter two groups at noon. The decrease in administration of scopolamine was thought advisable because of the high incidence of side reactions when the drug was given three times daily, as well as the relatively long duration of its action. Since 7.5 mg. of trihexyphenidyl daily produced few reactions, the dose was increased to 15 mg. daily for the return voyage. Capsules were administered for 60 hours rather than for 36 as on the outbound journey. Furthermore, the early morning capsule was given at 5:00 instead of at 6:00 a. m. This was done to decrease early morning vomiting. The capsule was given, and the subject immediately returned to bed until 6:00 a. m., when it was necessary to arise for breakfast. This gave 30 to 60 minutes for the medicament to exert its action before the day's activities were begun.

RESULTS

The incidence of nausea and vomiting among the various groups is given in table 1. Mild nausea includes all cases in which the person admitted discomfort due to the motion, but not of sufficient severity to cause him to miss a meal. Severe nausea was recorded only when one or more meals were missed during the period of medication and the subject reported himself close to vomiting.

It may be seen that on the outward trip the incidence of vomiting was greatly decreased by use of scopolamine, dimenhydrinate and diphenhydramine hydrochloride. There was no significant difference in the effectiveness of these compounds. Trihexyphenidyl at the dosage employed decreased the incidence of vomiting slightly. Neither pyranisamine maleate nor phenindamine tartrate afforded any demonstrable protection. Three of the seven persons in the series receiving diphenhydramine hydrochloride who vomited did so immediately on receiving

TABLE 1.—*Effectiveness of Various Drugs Against Seasickness*

	Placebo		Scopolamine Hydrobromide		Dimenhydrinate		Diphenhydramine Hydrochloride	Trihexyphenidyl		Pyranisamine Maleate	Phenindamine Tartrate	Chlorcyclizine Hydrochloride
No. subjects	80	74*	88	65*	82	66*	88	78	64*	76	79	63*
Mild nausea	32	17	25	19	33	27	22	28	31	30	23	28
Severe nausea	2	5	5	6	1	2	0	4	7	3	7	2
Vomiting	18	30	9	19	4	8	7	12	6	16	15	12
Per cent with vomiting	20	41	11	29	5	12	8	15	9	21	19	19
Per cent protected†	..	..	47	25	76	70	60	24	77	0	6	53

* Subjects on return journey.
† Per cent with vomiting in placebo group minus per cent with vomiting in drug group, divided by the per cent with vomiting in placebo group.

their 6:00 a. m. capsule. The previous medication had been 12 hours earlier. It is interesting to note that diphenhydramine hydrochloride gave the greatest degree of complete protection (no nausea).

The incidence of vomiting was considerably higher on the return trip than on the outbound voyage. More than 40 per cent of the group given placebos were affected, in contrast to half that percentage in the previous group. This increase was probably due to the longer duration of the experiment, as well as to the increased pitching encountered during the return voyage. Scopolamine as administered on the new dosage schedule gave only slight protection. Chlorcyclizine, trihexyphenidyl and dimenhydrinate all afforded significant protection at the 1 per cent probability level.

The relative effectiveness of the various drugs is strikingly demonstrated when the incidence of motion sickness in persons known to be susceptible is compared. Table 2 indicates the incidence of seasickness during the two trips among those who had been sick previously from

any form of motion (on the sea, in a car, train, airplane or amusement device), as revealed on the prevoyage questionnaire. Again, on the outward trip, diphenhydramine hydrochloride, dimenhydrinate and scopolamine (2.25 mg. daily) gave definite protection, trihexyphenidyl (7.5 mg. daily) some protection and pyranisamine maleate no protection. Phenindamine tartrate afforded approximately the same protection as trihexyphenidyl with this group, in contrast with the observations in table 1. On the return voyage dimenhydrinate and trihexyphenidyl (15 mg. daily) gave good protection to those persons with a history of previous motion sickness. Chlorcyclizine gave moderate but significant protection, whereas scopolamine (1.5 mg. daily) was ineffective. The susceptibility of this group is evidenced by the high incidence of sickness among the subjects given placebos, 11 of 14 vomiting. In contrast, only one and two subjects vomited among those receiving dimenhydrinate and trihexyphenidyl, respectively.

TABLE 2.—*Effectiveness of Drugs in Persons Known to Be Susceptible to Motion Sickness*

	Placebo		Scopolamine Hydrobromide		Dimenhydrinate		Diphenhydramine Hydrochloride	Trihexyphenidyl		Pyranisamine Maleate	Phenindamine Tartrate	Chlorcyclizine Hydrochloride
No. subjects	30	14*	37	12*	34	15*	29	20	12*	32	30	18*
Mild nausea	10	0	8	2	13	6	9	10	6	12	10	10
Severe nausea	2	1	4	1	1	1	0	4	2	2	1	0
Vomiting	10	11	3	8	2	1	1	5	2	9	5	6
Per cent with vomiting	33	79	8	67	6	7	4	17	17	28	17	33
Per cent protected†	..	..	73	15	82	92	89	48	79	16	50	58

* Subjects on return journey.
† See footnote † to table 1.

It was extremely difficult to differentiate such possible side effects of the drugs as dizziness, drowsiness, headache and mild nausea from symptoms induced by motion or the altered environmental conditions aboard ship. The total side effects reported for each of the groups are shown in table 3. On the outward trip, groups receiving scopolamine, dimenhydrinate and diphenhydramine hydrochloride each showed a lowered incidence of nervousness. This is probably correlated with the protection of these drugs against seasickness and, possibly, with a slight central depression. Surprisingly, however, there was no difference in the degree of drowsiness, regardless of the medicament. Phenindamine tartrate, which has slight stimulating properties, caused as high an incidence of drowsiness as diphenhydramine hydrochloride or dimenhydrinate. The only drug which increased insomnia was phenindamine tartrate. The incidence of blurred vision fell in line with the known parasympatholytic activity of the compounds. The highest proportion was in the group given scopolamine. Somewhat fewer cases appeared with trihexyphenidyl and phenindamine tartrate, and still fewer with

diphenhydramine hydrochloride and dimenhydrinate. There was no blurred vision among those receiving pyranisamine maleate, an observation in harmony with the low anticholinergic effect of this compound. No drug caused a significant increase of tinnitus or sweating. Contrary to expectations, the occurrence of dryness of the mouth did not follow the pattern of blurred vision. Scopolamine again was the chief offender, and trihexyphenidyl also brought about a significant increase, but there was no apparent change with phenindamine tartrate, diphenhydramine hydrochloride or dimenhydrinate. Surprisingly, this symptom was seen in a large number of subjects who received pyranisamine maleate. There was no striking pattern for the occurrence of diarrhea, constipation, fatigue, itching or rash. Headaches were slightly more numerous in the group given phenindamine tartrate. A single case of auditory hallucinations was discovered. This subject had received five doses of scopolamine (a total of 3.75 mg.) in 36 hours.

TABLE 3.—*Percentage Occurrence of Side Effects of Drugs Administered*

	Placebo		Scopolamine Hydrobromide		Dimenhydrinate		Diphenhydramine Hydrochloride	Trihexyphenidyl		Pyranisamine Maleate	Phenindamine Tartrate	Chlorcyclizine Hydrochloride
Nervousness	16	14*	5	11*	5	9*	4	16	20*	8	15	8*
Drowsiness	31	32	30	38	32	37	33	30	19	36	33	29
Insomnia	4	3	7	9	4	0	2	5	12	3	10	5
Blurred vision	1	9	27	26	5	12	7	14	50	0	18	17
Dryness of mouth	19	29	44	48	20	26	18	29	35	31	19	22

* These columns show percentages on return journey.

There was no striking difference in the drug reactions from dimenhydrinate and placebo on the return voyage (table 3). In general, the reactions to scopolamine and trihexyphenidyl were somewhat reduced and increased, respectively, as would be expected from the change in dosage. Chlorcyclizine produced a slight increase in blurred vision but no other side effects that differed from those seen with the placebos. Trihexyphenidyl produced a mild stimulation, as indicated by the increased nervousness and insomnia and the decreased drowsiness and fatigue. Its most serious effect was visual disturbance; 50 per cent of all subjects complained of blurred vision. This was considerably higher than with scopolamine. Similarly, ringing in the ears was relatively common on this voyage. On the other hand, the incidence of dryness of the mouth was only slightly greater than with the placebo and less than with scopolamine. Two cases of hallucinations were found in the group given trihexyphenidyl. One subject in each group reported a rash which he attributed to the drug.

In view of the dramatic relief of seasickness reported by Gay and Carliner [4] to result after dimenhydrinate therapy, we attempted to

evaluate this phase. All persons who vomited were given a capsule containing placebo, dimenhydrinate or scopolamine and observed after four to six hours. All persons who were severely nauseated but had not vomited were given placebos until they vomited or recovered. Table 4 includes data on only those receiving therapy after vomiting. Both scopolamine and dimenhydrinate showed a suggestive but insignificant superiority to placebos. The surprisingly high percentage of "cures" with placebos and the relatively few cases reported make it hazardous to attribute undue significance to these observations.

ELECTROENCEPHALOGRAPHIC STUDIES

Attempts have been made, unsuccessfully, to utilize electroencephalographic tracings as a means of preselecting susceptible persons.[14] To our knowledge, no records have been made while the motion sick person was at the height of his disturbance. To follow these possible electroencephalograhpic changes and to afford an objective measurement of

TABLE 4.—*Response to Seasickness Therapy*

	Placebo	Scopolamine * Hydrobromide	Dimenhydrinate †
No or slight improvement	15	15	23
Marked improvement	7	18	29
Per cent improvement	32	54 *	56 †

* P = 0.20, from chi-square test of difference from placebo group.
† P = 0.15, from chi-square test of difference from placebo group.

drug effects on the brain, a sturdy portable instrument was devised and used during the trip.

The recordings were made with a three channel Grass machine, the amplifiers being carefully protected against vibration and dislocation. The subject was examined in the sitting position with the electrode box close to his head. Specially constructed electrodes mounted on a headband were pressed against the scalp by a spring which connected headband and electrode. The three channels recorded simultaneously the activity from the occipital, parietal and frontal regions (monopolar leads). With the help of one assistant, about 30 to 70 seconds were required until headband and electrodes were adjusted and the recording was begun. Even in stormy weather perfect recordings were obtained from nearly every subject, and artefacts from rolling or pitching were

14. Jasper, H. H., and Morton, G., in the Proceedings of the Conference on Motion Sickness, Report no. C2508, National Research Council of Canada, June 6, 1943. Lindsley, D. B., and Wendt, G. R.: Civil Aeronautics Administration Report no. 40, 1944. Thorner, M. W., in the Minutes of the Sixth Meeting of the Sub-Committee on Motion Sickness, National Research Council, July 27, 1943, p. 80.

rare. The main difficulty was protecting the subject from falling off the chair or allaying his apprehension of doing so. Several unsatisfactory records were due to profuse sweating or trembling of seasick subjects. The subject was given a written explanation of the purpose of the test and allowed to observe the procedure on his predecessor, so that anxiety was largely forestalled. The eyes were kept closed during recording

TABLE 5.—*Electroencephalogram in Seasickness*

	Outbound						Inbound			
	First 48 Hr. With or Without Medication		Second 48 Hr. Without Medication		Last 48 Hr. Without Medication		First 3 Days With or Without Medication		Last 3 Days Without Medication	
Electroencephalographic Classification *	Severe Seasickness	Mild Nausea (31); Not Sick (35)	Severe Seasickness	Mild Nausea (73); Not Sick (21)	Severe Seasickness	Not Sick (77)	Severe Seasickness	Mild Nausea (35); Not Sick (8)	Severe Seasickness	Mild Nausea (5); Not Sick (68)
I	3	8	4	16	..	40	3	3	0	36
II	12	4	17	10	..	2	7	3	0	3
III	15	3	32	8	..	4	22	4	5	2
IV	6	46	8	37	..	21	6	23	0	23
V	1	5	9	23	..	10	2	10	3	9

* See text for classification.

TABLE 6.—*Electroencephalograms During Drug Administration*

	Placebo or No Pills		Diphenhydramine Hydrochloride, 150 Mg. Daily or Dimenhydrinate, 300 Mg. Daily		Scopolamine Hydrobromide, 1.5 or 2.25 Mg. Daily		Trihexiphenidyl, 15 Mg. Daily	
Electroencephalographic Classification	%	No.	%	No.	%	No.	%	No.
I	25	8	15	3	12	3	9	3
II	25	8	15	3	12	3	9	3
III	4	1	5	1	4	1	3	1
IV	45	11	50	10	80	20	60	20
V	16	4	25	5	4	1	28	9

except for occasional short periods. Allowing a brief observation of the normal routine served to reassure and relax the subject. The recordings were generally of two minutes' duration, with an occasional recording of five to 10 minutes.

The final evaluation of the records led to a division into five groups, as presented in tables 5 and 6. Group I (strictly normal alpha wave pattern) is defined by a dominant alpha frequency of 9 to 11 cycles per second, an alpha index of 30 to 80 per cent and an alpha activity in the frontal area of smaller amplitude than in the occipital. Group II (regular

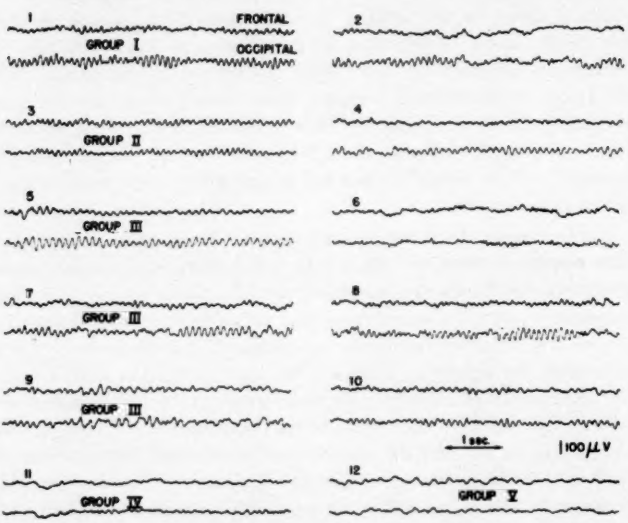
alpha pattern with high frontal alpha waves) is defined by an alpha index above 80 per cent, by amplitudes of not less than 25 microvolts and by a frontal alpha wave pattern the amplitude of which was about equal to or higher than that of the occipital regions. These electroencephalograms were similar to those obtained in the early stages of hyperventilation. Group III represents an alpha pattern with prominent slow wave component. In this group all electroencephalograms were included which either showed easily recognizable frequencies of 5 to 8 cycles per second, together with a dominant alpha wave pattern, or displayed a dominant wave frequency of below 9 cycles per second and an amplitude above 30 microvolts. Group IV includes all electroencephalograms of low voltage of either the low voltage fast wave type or the low voltage alpha type (alpha index of less than 30 per cent). Group V contains all electroencephalograms of low alpha voltage or discontinuous alpha activity associated with an irregular slow wave pattern; these electroencephalograms are similar to those obtained during drowsiness or fatigue. With this scheme, about 90 per cent of all tracings could be classified. Those which did not fall in any group were excluded from further consideration.

Table 5 gives the resulting compilation. Each subject is presented only once in any column. As will be noted, there is a pronounced difference between the electroencephalograms of subjects who showed severe symptoms of seasickness and those who either were mildly nauseated or or were free from any subjective symptoms of motion sickness. In the latter series the highest percentage of tracings belonged to groups IV and V. The number of subjects with drowsiness (group V) increased with the duration of the voyage, while at the conclusion of the voyage, when the sea was smooth and the majority had accustomed themselves to the life aboard the ship, tracings of group I dominated. On the other hand, the severely seasick persons more frequently presented a regular alpha wave pattern than did those who were not. They also showed an increasing number of tracings in group IV while seasickness persisted. Particularly in those tracings of group III on subjects whose seasickness had persisted were the electroencephalograms "abnormal" in terms of clinical electroencephalography, whereas during the first day of seasickness most tracings of group III would be designated as either "normal" or "borderline."

Furthermore, when seasickness had persisted for several days, an alpha rhythm was infrequently present and the slow waves became irregular and of low amplitude. These electroencephalograms were classified as of group III whenever an alpha pattern was present; otherwise they were placed in group V.

In the figure some typical tracings are assembled to illustrate the scheme of classification. The first five rows (left half) present the electroencephalograms (frontal and occipital) of seasick subjects who had vomited within an hour before the tracing was taken. All these subjects were severely nauseated during the recording. The right half of the figure shows the electroencephalograms of the same subjects at the end of the trip, when they had no or only minor complaints. Tracings in the last row give an example of group IV (left) and group V (right); both subjects were nauseated.

In table 6 an attempt was made to evaluate an effect of the drug on the electroencephalogram. Only those cases are included in which no



Typical electroencephalograms during motion sickness. Tracings *1, 3, 5, 7* and *9* are of different subjects during severe motion sickness. Tracings *2, 4, 6, 8* and *10* are from the same subjects after complete recovery. Tracings *11* and *12* are from two subjects who were nauseated. The significance of the various groups *(I* to *V)* is described in the text.

or only slight symptoms of seasickness were present. No significant results were obtained. With scopolamine and trihexyphenidyl low voltage alpha or low voltage fast wave activity (group IV) was encountered oftener than with placebos (16). On the other hand, with diphenhydramine hydrochloride and dimenhydrinate, a manifestation of drowsiness in the electroencephalogram (group V) was only slightly more frequent than with placebos and scopolamine, but about as frequent as with trihexyphenidyl.

COMMENT

It is apparent that prophylaxis against motion sickness is not related to the antihistaminic action of the drug. Pyranisaminemaleate was completely ineffective in doses giving strong antihistaminic action. Similarly, phenindamine tartrate gave, at most, only slight protection. The fact that certain antihistaminic drugs were effective must be attributed, therefore, to additional pharmacologic properties of these compounds. Their anticholinergic action represents the most likely cause, although the total effectiveness may not be accounted for on this basis. Diphenhydramine hydrochloride and dimenhydrinate were as effective as scopolamine, despite fewer peripheral manifestations of parasympathetic antagonism (dryness of the mouth, blurred vision, etc.), but recent studies on forced circling movements [15] suggest that they have important central atropine-like actions.

Diphenhydramine hydrochloride or dimenhydrinate seems the prophylactic of choice among the drugs studied in this experiment. Both scopolamine and trihexyphenidyl were remarkably effective in larger doses, but the high incidence of side effects makes them less desirable. Chlorcyclizine also gave significant protection and seems worthy of further investigation because of the low incidence of side effects. It had been expected that diphenhydramine hydrochloride and dimenhydrinate would produce considerable drowsiness in the large doses employed. Surprisingly, the incidence was no different from that in the placebo group. However, the amount of drowsiness reported in every group was high, probably obscuring any specific depressant effect of these drugs.

In contrast with the clearcut results obtained prophylactically, it was hard to evaluate the therapeutic data. Cures were somewhat, but not significantly, higher with both scopolamine and dimenhydrinate than with placebo. No other drugs were tried. However, acclimation to motion occurred rapidly, so that most persons reported improvement which they attributed to the medication. Approximately one third noted pronounced improvement within four to six hours after receiving a placebo. After the experimental period, capsules were given to anyone who requested them. Despite progressively increasing turbulence during the journey, only a few took the drug for the entire trip.

From the electroencephalograms it was learned that in the early phase of severe motion sickness cortical rhythms were not affected in such a way as to produce abnormal recordings in the clinical sense. There was, moreover, evidence of activation of the alpha rhythm and of slowing of the dominant wave frequency. To cite a single analogy, the electro-

15. Schiff, M.; Esmond, W. G., and Himwich, H. E.: Site of Action of Dramamine and Benadryl in Correction of Forced Circling Movements and of Convulsant Brain Wave Patterns Induced by Di-Isopropyl Fluorophosphate (DFP), Federation Proc. **9**:113, 1950.

encephalograms were similar to those taken in the early phase of hyperventilation, as certain symptoms, such as "lightheadedness" or "dizziness," are common to both conditions. On the other hand, the activation of the resting rhythms of the electroencephalograms by events in the lower parts of the brain might indicate a greater degree of "relaxation," as the motion sick patient is also passive and less responsive than normally. However, there was no suggestion from either questionnaire or electroencephalograms that the first symptom of motion sickness is drowsiness, as stated by Tyler and Bard.[1] The tracings indicated that drowsiness and fatigue develop with the persistence of the disorder. In certain cases of persistent motion sickness, the electroencephalogram may also show the abnormal dominance of a generalized slow wave pattern. The latter observation may be the result of the secondary effects of motion sickness, such as dehydration and lack of food.

SUMMARY

Scopolamine (hyoscine) hydrobromide, diphenhydramine (benadryl®) hydrochloride, dimenhydrinate (dramamine®), trihexyphemidyl (artane®) and chlorcyclizine (perazil®) hydrochloride were all notably effective in decreasing the incidence of seasickness of normal, unselected soldiers during a trans-Atlantic crossing aboard a United States Army transport. Phenindamine (thephorin®) tartrate and pyranisamine (neo-antergan®) maleate were ineffective. Among persons known to be susceptible to motion sickness, phenindamine tartrate showed a slight protective action, but was less beneficial than scopolamine, dimenhydrinate or diphenhydramine hydrochloride. Scopolamine and dimenhydrinate were tested therapeutically and found to be insignificantly effective. A lower, but nevertheless significant, incidence of relief was afforded with placebos alone.

Side effects were most frequent among those receiving 2.25 mg. of scopolamine hydrobromide or 15 mg. of trihexyphenidyl daily. Blurred vision and dryness of the mouth were the commonest complaints. One case of hallucinations was encountered with scopolamine and two with trihexyphenidyl. Tinnitus, insomnia and nervousness were also increased with trihexyphenidyl. Drowsiness was not increased with any medicament.

Seasickness caused an activation of the alpha rhythm of the electroencephalogram and a slowing of the dominant wave frequency. A pattern of drowsiness was particularly evident in cases of persistent seasickness. No significant changes could be detected as a result of the drug administration.

PHEOCHROMOCYTOMA AND ESSENTIAL HYPERTENSIVE VASCULAR DISEASE

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THAT essential hypertensive vascular disease may be clinically indistinguishable from the syndrome presented by certain patients with pheochromocytoma has been frequently and properly emphasized in recent years.[1] The pharmacologic actions of epinephrine, the only pressor agent which had been demonstrated in these neoplasms, could account for the so-called adrenal-sympathetic syndrome associated with paroxysmal hypertension but were hard to reconcile with a hemodynamic picture resembling essential hypertensive vascular disease. When epinephrine is infused into a normal man at a rate sufficient to produce a systolic blood pressure of 180 mm. Hg, there is usually no significant

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1. (*a*) Thorn, G. W.; Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of the Adrenal Associated with Persistent Hypertension, Ann. Int. Med. **21**:122, 1944. (*b*) Green, D. M.: Pheochromocytoma and Chronic Hypertension, J. A. M. A. **131**:1260 (Aug. 17) 1946. (*c*) Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, ibid. **135**:971 (Dec. 13) 1947. (*d*) Smithwick, R. H.; Greer, W. E. R.; Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma, New England J. Med. **242**:252, 1950.

elevation of diastolic pressure, and the infusion is accompanied with a number of unpleasant symptoms, such as anxiety and palpitation; further increase in the rate of epinephrine administration is often marked by the appearance of extrasystoles, restlessness and hyperpnea. Another striking variance from the picture of essential hypertensive vascular disease is the fact that piperoxan hydrochloride (formerly piperidyl-

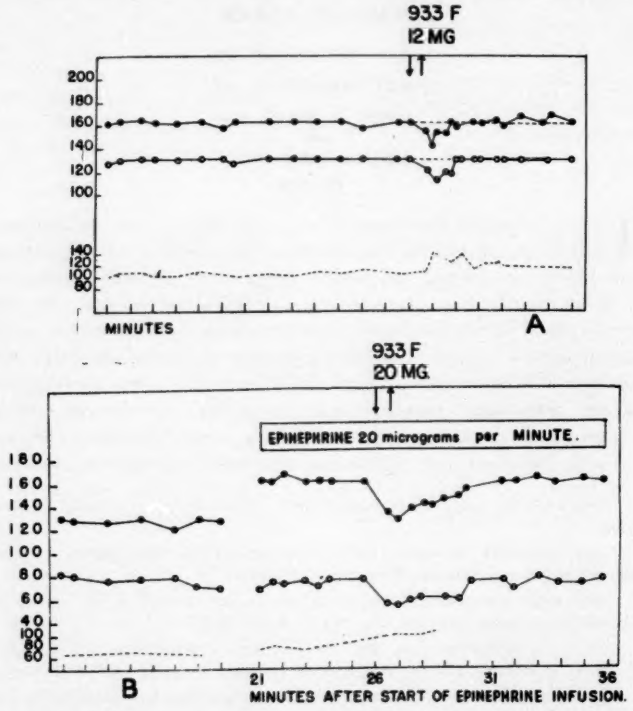

Fig. 1.—Demonstration of attempt to reproduce (*A*) the hypertension observed in a boy (case 15) 12 years of age with pheochromocytoma before operation (*B*) by epinephrine infusion in a normal subject (a man, aged 23). No significant increase of diastolic blood pressure could be obtained by a continuous intravenous epinephrine infusion with doses producing an equal systolic pressure. The difference in response to 10 mg. of piperoxan hydrochloride (933 F) per square meter of body surface is apparent.

methyl benzodioxane, or 933F) injected intravenously during such an infusion causes a pronounced fall in blood pressure to levels equal to or lower than those observed prior to the start of the epinephrine infusion.

The marked glycogenolytic action of epinephrine usually produces hyperglycemia, and this feature is frequently not present in those cases or stages of pheochromocytoma most closely resembling essential hypertensive vascular disease.

Our studies of a patient with a pheochromocytoma [1c] whose blood pressure was 160/128, who showed no hyperglycemia and who exhibited a comparatively feeble response to piperoxan hydrochloride (depression in blood pressure only to 138/110) focused our attention on these dissimilarities (fig. 1).

The finding in 1949 [2] that the primary amine arterenol (norepinephrine) constituted a proportion of the catechol content of these neoplasms which might range as high as 97 per cent seemed to promise an explanation more consonant with the observed phenomena. This substance (fig. 2), which is also present in significant amounts in

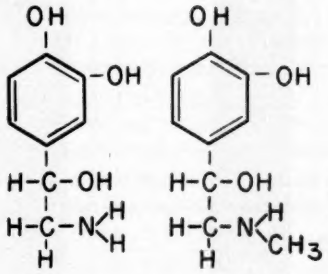

Fig. 2.—The formula of arterenol (nor-epinephrine, nor-adrenaline) is on the left and that of epinephrine on the right.

the normal adrenal medulla,[2b] has physiological actions in man that might well produce a clinical picture similar to the one presented by the patient described above. The hemodynamic effects of arterenol were studied in man [3] and contrasted with those of its methylated congener, epinephrine. The amines were administered by continuous intravenous infusion; the right side of the heart was catheterized, and cardiac output was determined by the Fick principle; intra-arterial pressures were optically recorded with the Hamilton manometer. The infusion of

2. (*a*) Holton, P.: Nor-Adrenaline in Adrenal Medullary Tumours, Nature, London **163**:217, 1949. (*b*) Goldenberg, M.; Faber, M.; Alston, E. J., and Chargaff, E. C.: Evidence for the Occurrence of Nor-Epinephrine in the Adrenal Medulla, Science **109**:534, 1949.

3. Goldenberg, M.; Pines, K. L.; Baldwin, E. deF.; Greene, D. G., and Roh, C. E.: The Hemodynamic Response of Man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension, Am. J. Med. **5**:792, 1948.

arterenol was followed by a prompt increase in both systolic and diastolic blood pressures due to an impressive augmentation of total peripheral resistance. Cardiac output was little affected, and the subjects were so strikingly free of symptoms as to be frequently unaware that any change had occurred in their vascular dynamics (fig. 3). The hypertensive effect of equal amounts of epinephrine, on the other hand, was due primarily to a large increase in cardiac output which overbalanced the constantly observed decrease in total peripheral resistance; it was usually accompanied with tachycardia, palpitation and other symptoms. Epinephrine caused a considerably greater increase

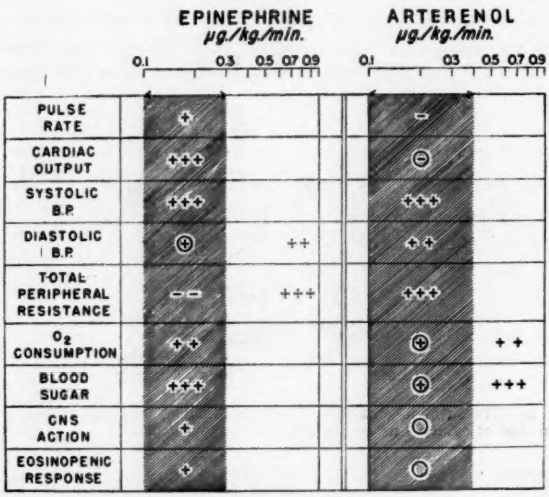

Fig. 3.—Comparison of effects of a continuous intravenous infusion of epinephrine and arterenol. Shaded areas indicate data from studies by Goldenberg and others,[3] Goldenberg and Aranow,[5] Cori and Buchwald[6] and Madison (J. Clin. Investigation **29**:789, 1950). Data reported in light areas are derived from present observations on patients with pheochromocytoma. Plus signs indicate degree of response; circles indicate response was insignificant; light plus signs indicate preoperative findings.

in metabolic rate than did arterenol, and other experiments have demonstrated that its glycogenolytic action is four to eight times as great as that of the primary amine (rabbit,[4] man[6]). On the other hand, epinephrine in doses too small to cause an increase of blood pressure may produce hyperglycemia. The relation of minimal hyperglycemic to

4. McChesney, E. W., and McAuliff, J. P.: Unpublished data.

5. Goldenberg, M., and Aranow, H., Jr.: Unpublished data.

minimal pressor doses differs from species to species. In unanesthetized rabbits 0.05 microgram per kilogram of body weight per minute produces hyperglycemia, whereas 0.6 microgram per kilogram per minute is the minimal pressor dose. In man, 0.025 microgram per kilogram of body weight per minute is the minimal hyperglycemic dose and 0.05 microgram per kilogram per minute is the minimal pressor dose.[6]

Data obtained from experiments on animals suggested that the pressor action of arterenol would be blocked by piperoxan hydrochloride to a much less degree than that of epinephrine.[7] When experimental hypertension was produced in 19 normotensive human subjects by the controlled intravenous infusion of arterenol, and piperoxan hydrochloride injected without altering the rate of arterenol administration, a much greater inhibition of the pressor effect of the latter was observed than had been anticipated from these animal data. Finally, a strongly positive reaction to the test with piperoxan hydrochloride was twice recorded in a patient whose tumor contained for practical purposes arterenol only (97 per cent of the catechol fraction).[8] The epinephrine content of this tumor was less than that of a normal adrenal medulla (in case 12 the weight of the tumor was 79 Gm.; 0.03 mg. per gram of epinephrine and 1.02 mg. per gram of arterenol were present).

It became clear, therefore, that the feeble response to piperoxan hydrochloride observed in the patient first mentioned could not be adequately explained by the fact that the circulating pressor agent was predominantly arterenol rather than epinephrine.

Recently, a correlation of the wide spectrum of clinical manifestations of pheochromocytomas with the varying content of epinephrine and arterenol in these tumors was attempted.[9] As more cases were analyzed, it was found that the correlation was less good than it had first appeared. Our clinical studies of 18 patients with pheochromocytoma with persistent hypertension and the chemical analysis of the tumors of 10 of them form the basis of this paper.

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6. Cori, C. F., and Buchwald, K. W.: Effect of Continuous Intravenous Injection of Epinephrine on the Carbohydrate Metabolism, Basal Metabolism and Vascular System of Normal Men, Am. J. Physiol. **95**:71, 1930.

7. Stehle, R. L., and Ellsworth, H. C.: Dihydroxyphenyl Ethanolamine (Arterenol) as Possible Sympathetic Hormone, J. Pharmacol. & Exper. Therap. **59**:114, 1937.

8. Goldenberg, M., and Aranow, H., Jr.: Diagnosis of Pheochromocytoma by the Adrenergic Blocking Action of Benzodioxan, J. A. M. A. **143**:1139 (July 29) 1950.

9. Goldenberg, M., and Aranow H., Jr.: Epinephrine and Nor-Epinephrine in Pheochromocytoma, read at the twenty-second annual meeting of the American Heart Association, Atlantic City, N. J., June 3-4, 1949.

METHODS

The arterenol and epinephrine contents of the pheochromocytomas from 10 patients with persistent hypertension and from four patients with paroxysmal hypertension were determined by chemical methods. Paper partition chromatography [10] and a modification of von Euler's colorimetric method [11] were employed.

The tumor specimens were extracted with acid alcohol (1 per cent), and the separation of epinephrine and arterenol on filter paper was obtained by the use of a mixture of phenol, 8-hydroxyquinoline and water as solvent. The papers were air dried, and potassium ferricyanide was used as indicator. Adrenochrome and noradrenochrome were then formed and gave characteristic colors. A quantitative estimation by planimetry of the epinephrine and arterenol spots is feasible.[2b] The quantitative estimation by paper chromatography was abandoned as a routine measure when it became clear that von Euler's colorimetric method could be simplified by omitting adsorption. The former method still had to be used to determine small epinephrine fractions in tumors containing more than 95 per cent arterenol.

Von Euler's colorimetric method is based on the fact that epinephrine can be easily oxidized by 0.1 normal iodine at p_H 4.0, with formation of iodoadrenochrome, whereas at this p_H only about 10 per cent of arterenol is oxidized. At p_H 6.0 epinephrine and arterenol are fully oxidized. The specimens of tumors were extracted with equal volumes of 10 per cent trichloracetic acid, and, instead of following this up with adsorption procedures on aluminum hydroxide, as recommended by von Euler, the extracts were diluted, brought to p_H 4.0 and then evaluated colorimetrically. The specificity of the method rests on the chromatographic proof that no other color-producing compounds were formed on oxidation.

Comparison of the results obtained by the chemical methods with those of bioassays showed that the pressor activities of these neoplasms could be completely accounted for by their content of epinephrine and arterenol and that the tumors contained no other pressor agent in significant amounts.

RESULTS

Correlation of clinical and chemical data indicated that tumors which contained small total amounts of arterenol and insignificant quantities of epinephrine caused a clinical picture closely resembling essential hypertensive vascular disease. Metabolic disturbances, on the whole, were of secondary importance, although one of the patients showed a significant increase of basal metabolic rate (table 1, cases 12 and 14).

CASE 14.—B. B. (PH 677501), a married white man, was 59 years of age in December 1948, when he was admitted to the Presbyterian Hospital, New York, for treatment of congestive heart failure. Thirteen years previously asymptomatic hypertension had been discovered in the course of a routine life insurance examination. Two years later, when the patient was 48, he began to have severe attacks characterized by occipital headaches, pounding in the ears, vomiting and sweating.

10. James, W. O.: Demonstration and Separation of Noradrenaline, Adrenaline and Methyladrenaline, Nature, London **161**:851, 1948. Goldenberg and others.[2b]

11. von Euler, U. S., and Hamberg, U.: Colorimetric Estimation of Noradrenalin in the Presence of Adrenalin, Science **110**:561, 1949.

Bouts such as these recurred every few months, were of several hours' duration, could be relieved by administration of analgesics and were not accompanied with any significant change in the level of arterial pressure from that observed between attacks.

He was first seen by a member of the staff in 1942, at which time an arterial tension of 220/130 and an accentuated second aortic heart sound were the only noteworthy abnormalities recorded. Funduscopic studies performed during the following year revealed grade 3 hypertensive changes in the retinas. He was seen frequently between 1942 and 1944 and was usually asymptomatic. The blood pressure ranged from 180/105 to 240/140. An observation was made during an "attack," and the pressure was recorded as 230/130. The attacks disappeared in 1944 and did not recur during the remainder of his life.

TABLE 1.—*Correlation of Chemical and Clinical Findings in Ten Cases of Pheochromocytoma with Persistent Hypertension*

Hospital	Case No.*	Blood Pressure, Mm./Hg	Pulse Rate	Fasting Blood Sugar, Mg./100 Cc.	BMR, %	933F Response	Weight of Tumor, Gm.	Epinephrine, Mg./Gm.	Arterenol, Mg./Gm.	Epinephrine, %	Arterenol, %
N. Y. H.....	10	170/110	130	245	Not determined	+	567	5.9	2.5	70	30
N. Y. H.....	9	180/120	84	250	+21; +40; +7	+	545 (½ blood)	6.52	1.27	84	16
Presb. H.....	6	240/130	120	92	+38	+	55	8.17	1.4	86	14
Mont. H.....	11	240/140	84	282	+47	+	39.5	7.65	2.02	79	21
Mass. Mem. H..	7	214/138	...	120	(+64) +1	—	...	2.08	0.95	68	32
Pol. H.....	5	190/130	80	167	+18	+	62	3.6	4.1	47	53
Pass. Mem. H...	8	170/120	100	135; diabetic curve	Not determined	+	...	3.68	6.96	35	65
Presb. H.....	13	130/100	140	222	Not determined	Not determined	180	0.44	3.2	12	88
Bost. City H....	12	240/130	72	120 to 140	+31; +52	+	79	0.08	1.02	8	97
Presb. H.....	14	180/115	88	Not determined	Not determined	Not determined	21	0.38	3.45	10	90
Presb. H.....	15	Nonfunctioning thoracic pheochromocytoma							Adrenochrome only!		

* Tumors in cases 10, 9, 6, 11 and 7 contained predominantly epinephrine; tumors in cases 5, 8, 13, 12 and 14 contained predominantly arterenol.

From 1944 to 1948 he experienced no symptoms referable to the cardiovascular system but displayed severe involutional melancholia in the latter part of 1947. This responded well to electric shock therapy.

In the spring of 1948, his blood pressure was 195/125 and his heart was enlarged and at times showed a diastolic gallop rhythm. Three months prior to his hospital admission he began to have precordial pain on exertion, which was relieved by rest and administration of glyceryl trinitrate, and a month before his admission evidences of congestive heart failure became manifest.

At the time of his admission, in December 1948, he exhibited Cheyne-Stokes respiration, conspicuous cardiac enlargement, rales at the bases of the lungs and hepatomegaly. The blood pressure was 180/115. The conventional measures for the management of congestive failure were instituted, but the patient died suddenly two days later. The suspicion of pheochromocytoma had never been entertained.

At autopsy a pheochromocytoma of the left adrenal gland was observed which weighed 21 Gm. It contained 0.38 mg. per gram of epinephrine and 3.45 mg. per

gram of arterenol; i.e., epinephrine constituted only 10 per cent of the pressor substance in the tumor and arterenol 90 per cent.

Generalized severe arteriosclerosis and arteriolosclerosis were present, with extensive cerebral arteriosclerosis and multiple old areas of encephalomalacia of the cerebellum. The expected evidence of chronic passive congestion and moderately severe arteriolonephrosclerosis were present.

Case 12.—N. B. (CH 1340900),[12] a 22 year old, single waitress, was admitted to the hospital for evaluation of asymptomatic hypertension which had been discovered 2½ months earlier on a routine preemployment physical examination. Her local physician had recorded blood pressures ranging from 170 to 190 mm. Hg systolic and 120 to 130 diastolic. Symptoms of hypermetabolism were not impressive, but the determination of a basal metabolic rate of + 31 per cent led to the administration of propylthiouracil, which had no significant effect on the clinical picture.

Physical examination on her admission to the hospital revealed blood pressures of 230/140 and 240/130 in the arms and 200/170 in the legs. The pulse rate was 72. Save for the finding of a soft rounded 5 cm. mass in the right upper quadrant of the abdomen and minimal arteriolar narrowing in the optic fundi, there were no other noteworthy observations. Palpation of the abdominal mass did not alter the blood pressure level.

Relevant laboratory findings included the following: Fasting blood sugar values ranged from 120 to 140 mg. per 100 cc.; three basal metabolic rates were determined as +31, + 31 and + 52 per cent, and an abdominal roentgenogram showed calcification in the region of the right adrenal gland, as well as slight downward displacement of the right kidney. Two tests with piperoxan hydrochloride gave positive results.

At operation a pheochromocytoma was removed which weighed 79 Gm. Chemical analysis of this tumor revealed 1.02 mg. of arterenol per gram of tumor tissue and only 0.03 mg. per gram of epinephrine.

As the total amount of arterenol in the tumor increases, additional evidences of hypermetabolism and hyperglycemia are to be expected, although arterenol causes these to a much less degree than an equal amount of epinephrine (cases 5, 8 and 13, table 1). When the predominant catechol in the neoplasm was epinephrine, hypertension, hypermetabolism, hyperglycemia and tachycardia occurred, but in a given patient they were not necessarily constantly present (cases 6, 7, 9, 10 and 11, table 1).

Case 11.—Z. Z. (MH 49195),[13] a 50 year old white man whose right eye had been blind from birth, was admitted to the Montefiore Hospital, New York, in October 1949 because of "spells" of blindness, vertigo and sweating of four years' duration.

In 1938 the patient experienced a brief bout of substernal pain which his local physician diagnosed as due to a myocardial infarction. After a short period of rest, he returned to work and was free of symptoms until the end of 1944, when attacks of vertigo, headache and pain and loss of vision in the left eye occurred.

12. Dr. Reginald H. Smithwick and Dr. Charles W. Robertson gave permission for use of these data.

13. Dr. Leo Leiter gave permission for use of these data.

Hypertension was not present at this time. Basal metabolic rates of + 75 and + 125 per cent were recorded by his local physician and led him to institute therapy for disease of the thyroid. The attacks began to include sharp retrosternal pain and sweating and seemed somewhat benefited by thiouracil administration.

An acute mental breakdown in 1946 responded well to 12 electric shock treatments.

In 1947 systolic hypertension was first noted, and later in that year the patient was admitted to the Brooklyn Jewish Hospital because of an attack of retrosternal pain, accompanied with a small hemoptysis. Glycosuria and hyperglycemia were noted and led to the diagnosis of diabetes mellitus; the patient was placed on a diet and given protamine zinc insulin. At this time his systolic blood pressure was observed to be 200 mm. Hg, and values approximating this were recorded from then on. He was discharged from the hospital with the diagnosis of myocardial infarction due to arteriosclerotic coronary thrombosis.

An attack of pulmonary edema in March 1949, accompanied with hemoptysis, led to digitalization and salt restriction.

When admitted to Montefiore Hospital seven months later, physical examination revealed him to be acutely ill, apprehensive and hyperactive. He was well developed and nourished, and there was profuse generalized sweating. The blood pressure was 240/140 and the pulse rate 84. The fundi showed grade 3 hypertensive changes in the retinas. The left border of cardiac dulness reached the anterior axillary line.

Laboratory examinations disclosed a white blood cell count of 13,400, glycosuria (4 +) and albuminuria (1 +), a fasting blood sugar level of 282 mg. per 100 cc., a diabetic dextrose tolerance curve, normal values for serum electrolytes, a basal metabolic rate of + 47 per cent, with a normal uptake of radioiodine, and a serum cholesterol content of 296 mg. per 100 cc. He excreted 7.6 mg. of 17-ketosteroids in 24 hours. Renal plasma flow was observed to be 434 cc. per minute, and the glomerular filtration rate was 132 cc. per minute. This indicated a filtration fraction of 0.304.

During spontaneous "attacks" the patient's blood pressure rose from its level on his admission to values exceeding 300/200, and similar attacks were induced by the administration of both histamine and tetraethyl ammonium chloride. The test with piperoxan hydrochloride gave a positive reaction. Perirenal aerograms taken prior to the patient's admission were thought to suggest the presence of a tumor in the right adrenal area.

A pheochromocytoma of the right adrenal area, weighing 39.5 Gm., was operatively removed; it contained 7.65 mg. per gram of epinephrine and 2.02 mg. per gram of arterenol.

Following the operation the patient's condition was greatly improved. His glycosuria disappeared, and his dextrose tolerance curve became normal. Tests with piperoxan hydrochloride, histamine and tetraethyl ammonium chloride all gave normal reactions. A labile hypertension ranging from 150/80 to 180/110 persisted for four months (while the patient was under observation at Montefiore Hospital).

It is noteworthy that in this case paroxysmal hypertension combined with persistent hypermetabolism preceded the development of persistent hypertension. Similar observations were made in another patient (case 10), in whom diabetes antedated the establishment of persistent hypertension by a number of years. This may well be due to the fact that

metabolic effects are produced by much smaller doses of epinephrine than are required to produce hypertension.[6]

In the studies on the action of epinephrine and arterenol cited above,[3] it was demonstrated in man that doses of epinephrine up to 0.3 microgram per kilogram of body weight per minute produced a systolic hypertension which was due to an increase in cardiac output rather than to an augmentation of peripheral resistance. Our studies suggest that with larger doses epinephrine also causes over-all vasoconstriction in man. This view is supported by experiments performed on A. C. (case 5) before and four months after her pheochromocytoma was operatively removed.[14] When epinephrine in amounts up to 0.34 microgram per kilogram per minute was infused into this patient four months postoperatively, her systolic blood pressure increased from 129

TABLE 2.—*Blood Pressure Changes in a Patient with Pheochromocytoma (Case 5, Table 1)*

During Epinephrine Infusion			During Arterenol Infusion		
Dose, Microgram/ Kg./Min.	Blood Pressure, Mm. Hg		Dose, Microgram/ Kg./Min.	Blood Pressure, Mm. Hg	
	Systolic	Diastolic		Systolic	Diastolic
Preoperative:					
0	197	134	0	198	130
0.16	196	134	0.10	208	138
0.30	210	148	0.18	222	147
0.60	232	160	0.22	226	145
....	...	...	0.38	244	150
Postoperative:					
0	129	88	0	123	81
0.25	152	80	0.024	133	96
0.34	158	82	0.07	150	110
....	...	..	0.10	162	117

mm. Hg to 158, and her diastolic blood pressure fell from 88 mm. Hg to 82. This is an example of "cardiac output hypertension" (table 2). A similar infusion administered preoperatively indicated a much higher threshold, probably because of the presence of large amounts of epinephrine already in the circulation. Administration of 0.3 microgram of epinephrine per kilogram per minute increased the systolic pressure from 190 to 210 and raised the diastolic pressure from 134 to 148. When the rate of administration was increased to 0.6 microgram per kilogram per minute, the pressure rose to 232/160. This type of diastolic hypertension could be produced in normal man with impunity only with comparable doses of arterenol; alarming side reactions prohibited the use of such large doses of epinephrine in the normal subject. Table 2 also indicates the increase in sensitivity to arterenol shown by this patient after the removal of the tumor, which weighed 62 Gm. and

14. Goldenberg, M., and Pomerantz, N.: Unpublished data.

contained 3.6 mg. per gram of epinephrine (47 per cent of the total catechol) and 4.1 mg. per gram of arterenol (53 per cent).

In our experience tumors containing large amounts of either epinephrine or arterenol usually produced a clinical picture characterized by diastolic hypertension, associated with significant metabolic disturbances, i. e., hypermetabolism, weight loss and hyperglycemia (cases 5, 8, 9, 10, 11 and 13). Only small tumors which contained arterenol predominantly (90 to 97 per cent) and not more than a total of 80 mg. of this catechol gave a syndrome mimicking essential hypertensive vascular disease with unimpressive metabolic features (cases 12 and 14, fig. 3 and table 1).

A surprising observation was that patients with tumors containing large quantities of epinephrine may, at times, present a clinical picture indistinguishable from that of essential hypertensive vascular disease, with normal heart rate, absence of hyperglycemia, absence of metabolic disturbance as indicated by normal basal oxygen consumption and a negative or equivocal response to piperoxan hydrochloride. This suggested that persistent hypertension in patients with pheochromocytoma need not at all times be due to the presence in the circulation of sufficient quantities of arterenol or epinephrine to cause hypertension by direct cardiovascular action, i. e., of the sort seen in the acute infusion experiment. Although each of the indicators used—heart rate, basal metabolic rate, fasting blood sugar level and piperoxan reaction—has its limitations, when all four are normal it appears highly unlikely that significant amounts of epinephrine or arterenol are circulating. A patient with such a condition is described.

Case 7.—D. N. (MMH 335866),[12] a 35 year old married white woman was admitted to the hospital with a history of loss of vision in the right eye of two weeks' duration. Two years prior to entry she had noted attacks consisting of the gradual development of nausea, followed by palpitation, severe headache and vomiting. Attacks usually lasted three to four hours and were of almost daily occurrence until 10 months before her admission, when their frequency decreased. Seven months prior to hospitalization a systolic blood pressure of 270 mm. Hg was noted, but, save for the attacks, she remained asymptomatic until two weeks before entry, when the vision of the right eye became severely impaired. The basal metabolic rate at this time was + 64 per cent, and funduscopic examination revealed hemorrhages.

The blood pressure on her admission was 214/138, and grade 3 hypertensive changes in the retinas were noted. The basal metabolic rate at the time of her admission had fallen to + 1 per cent, and a test with piperoxan hydrochloride gave a negative reaction. The fasting blood sugar value was 120 mg. per 100 cc.

At operation a pheochromocytoma measuring 6 by 5 cm. containing 2.08 mg. of epinephrine per gram of tumor tissue was removed; epinephrine constituted 68 per cent of the total catechol content.

Follow-up studies on 12 patients with pheochromocytoma associated with persistent hypertension, after their chromaffin tumors had been

successfully excised, provided strong corroboration for the concept that hypertension in patients with chromaffin tumors may not at all times

TABLE 3.—*Hypertension Observed After Removal of Tumor in Seven of Twelve Cases of Pheochromocytoma*

Hospital	Case No.	Age	Duration of Symptoms, Yr.	Blood Pressure, Mm. Hg		Fasting Blood Sugar, Mg./100 Cc.		BMR, %	Piperoxan Reaction		Duration of Postop. Hypertension
				Preop.	Postop.	Preop.	Postop.	Preop.	Preop.	Postop.	
Mass. Mem. H..	7	35	2	214/138	160/100	120	....	(+64) +1	—	..	5 days
N. Y. H.....	10	56	10	170/110	Fluct. 170/110	245	Normal	.....	+	—	19 days; no further data available
Presb. H.....	2	13	3	180/120	160/116	215	Normal	+56	+	—	4 wk.
Pass. Mem. H...	8	31	6	170/120	150/110	135	....	.....	+	—	11 wk.; no further data available
Mont. H.....	11	50	5	240/140	Fluct. 210/110	282	Normal	+47	+	—	4 mo. under observation
Presb. H.....	6	49	1	240/130	174/130	92	....	+38	+	—	6 mo. under observation
Presb. H.....	17	29	2	240/140	200/110	132	Normal	(+2) +25	Not determined	—	7 yr. under observation

TABLE 4.—*Pheochromocytoma Associated with Paroxysmal Hypertension*

Hospital	Case No.	Weight of Tumor, Gm.	Epinephrine Content of Tumor, Mg./Gm.	Arterenol Content of Tumor Mg./Gm.	Epinephrine, %	Arterenol, %
V. A. H. (Bronx).....	19	92	4.1	6.0	40	60
Presb. H.....	20	332	7.5	8.8	46	54
V. A. H. (San Francisco)	21	790	0.15	4.8	3	97
Mass. Gen. H.....	22	...	9.1	7.2	56	44

TABLE 5.—*Data on Six Additional Tumor Specimens Analyzed After Manuscript Was Completed*

Hospital	Case No.	Epinephrine Content of Tumor, Mg./Gm.	Arterenol Content of Tumor, Mg./Gm.	Epinephrine, %	Arterenol, %
Pheochromocytoma Associated with Persistent Hypertension					
Johns Hopk. H.....	23	0.41	5.65	7	93
Mt. Si. H. (N. Y.).....	24	0.11	4.53	2	98
Bridg. H.....	25	1.95	5.8	25	75
Pheochromocytoma Associated with Paroxysmal Hypertension					
Johns Hopk. H.....	26	0.17	6.85	2.4	97.6
Johns Hopk. H.....	27	6.00	4.72	54	46
V. A. H. (Richmond, Va.)	28	0.29	4.92	6	94

Drs. E. Calkins, Baltimore, A. F. Delevett, Bridgeport, Conn., J. L. Gabrilove, New York, and C. F. Wingo, Richmond, Va., supplied portions of these tumors.

be dependent on an increased quantity of circulating pressor catechols. In seven of the 12 patients hypertension continued to be present for varying lengths of time after the removal of the neoplasm, although all of them showed striking clinical improvement (table 3).

Blood sugar levels returned to normal, lost weight was regained and piperoxan reactions which were positive prior to operation became negative. It is worthy of note that in two patients normotensive levels were reached and maintained after intervals which ranged from five days to four weeks.

No significant difference was found in the catechol content of the tumors removed from patients exhibiting paroxysmal hypertension, as contrasted with that of the neoplasms of patients with persistent hypertension. The epinephrine content varied from 3 to 56 per cent and the arterenol content from 44 to 97 per cent. The total amounts of catechol were comparable in the two groups (table 4).

COMMENT

These observations indicate that intermittent, as well as continuous, discharge of the pressor substances may be associated with persistent hypertension. It appears that when significant amounts of either epinephrine or arterenol have been present in the circulation for long periods hypertension may be initiated which does not require these circulating agents for its maintenance. This view is supported by the fact that seven of our 12 patients with pheochromocytoma remained hypertensive for varying lengths of time after operative excision of their tumors. Whether this sustained hypertension is due to a specific action of epinephrine or arterenol, or simply due to the fact that blood pressure increases, if frequent and of long enough duration, may outlive the stimuli which cause them, is impossible to decide from presently available data. The mechanism may be analogous to that which causes the persistence of experimental audiogenic hypertension in rats after the auditory stimulation has stopped.[15]

It is tempting to speculate that in pheochromocytoma we may be dealing with a model experiment of essential hypertensive vascular disease in that in the latter condition frequent or prolonged secretion of adrenergic agents may be analogous to the secretion of catechols by the tumor, thus setting into action a self-perpetuating mechanism. The body of evidence suggesting the identity of arterenol and sympathin-N [16] makes the speculation more provocative.

15. Medoff, H. S., and Bongiovanni, A. M.: Blood Pressure in Rats Subjected to Audiogenic Stimulation, Am. J. Physiol. **143**:300, 1945. Farris, E. J.; Yeakel, E. H., and Medoff, H. S.: Development of Hypertension in Emotional Gray Norway Rats After Air Blasting, ibid. **144**:331, 1945. Smirk, F. H.: Pathogenesis of Essential Hypertension, Brit. M. J. **1**:791, 1949.

16. von Euler, U. S.: A Specific Sympathomimetic Ergone in Adrenergic Nerve Fibers (Sympathin) and Its Relation to Adrenaline and Nor-Adrenaline, Acta physiol. Scandinav. **12**:73, 1946.

It seems possible to us that the problem of essential hypertensive vascular disease may not be "What causes it?" but "What perpetuates it after the primary stimulus has ceased?"

SUMMARY

Eighteen patients who had pheochromocytoma with persistent hypertension and four patients who had pheochromocytoma with paroxysmal hypertension were subjected to clinical analysis. Fifteen of the tumors were analyzed by chemical means.

Total epinephrine and/or arterenol content and the ratio of epinephrine to arterenol did not differ essentially in the two groups.

In the patients who had pheochromocytoma with persistent hypertension the following correlation could be established:

A. When the tumor contains epinephrine predominantly, or a large amount of arterenol, the picture is characterized by hypertension, tachycardia, hyperhidrosis, hypermetabolism and, frequently, hyperglycemia. Tests with piperoxan hydrochloride give positive reactions.

B. When the tumor is small and contains for practical purposes arterenol only, the syndrome of essential hypertensive vascular disease is closely mimicked. An increase in basal metabolic rate may be present, and the test with piperoxan hydrochloride gives a positive reaction.

This correlation is limited in that, in certain stages of the disease, no evidence of increased circulating catechols (epinephrine and arterenol) can be obtained; i. e., hypertension may be present, with normal basal metabolic rates, normal pulse rates, lack of hyperglycemia and negative piperoxan reactions.

Intermittent, as well as continuous, secretion of the catechols by the tumor may lead to persistent hypertension.

Hypertension persisted for varying periods in seven of 12 patients whose chromaffin tumors were operatively excised, although all other clinical signs regressed promptly. This corroborates the view that excessive amounts of circulating catechols need not be constantly present to maintain the elevation in blood pressure initially produced by them ("secondary hypertension").

The possible relation of "secondary hypertension" in pheochromocytoma to essential hypertensive vascular disease is discussed.

CURRENT CONCEPTS OF MALARIA

With a Review of Five Hundred and Ten Admissions to a Veterans Hospital

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ASPINWALL, PA.

INCIDENCE, ECONOMIC SIGNIFICANCE AND MILITARY IMPORTANCE OF MALARIA

MALARIA is an important disease in the United States and the world. It is widely distributed in all tropical and subtropical countries and over many temperate regions. Prevalence of the different etiological agents varies somewhat geographically. Plasmodium vivax (the vector of tertian malaria) has the widest distribution and is the prevailing species in temperate zones. Plasmodium malariae (the cause of quartan malaria) is comparatively rare; it is mainly a parasite of subtropical and temperate areas. Plasmodium falciparum (the agent of malignant tertian malaria) is encountered chiefly in heavily infected districts in the warmer parts of the world, and the disease it causes has been called "tropical malaria." These three are the important malarial parasites for the human race. Plasmodium ovale is a rare species which causes a mild form of tertian malaria. Plasmodium knowlesi is normally a parasite of rhesus monkeys but has on many occasions been inoculated into man, particularly in the treatment of dementia paralytica.

A study conducted in 1932, based on reports from only 65 countries, showed that a total of 17,750,760 patients with malaria were treated dur-

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ing that year.[1] This did not give a complete idea of the number of cases actually existing, since it is practically impossible to make complete surveys in certain tropical countries. Today the estimated incidence is 300,000,000 cases annually, with 3,000,000 deaths.[2] Control of malaria has been assigned first priority by the World Health Organization. This disease is costing the world $175,000,000 each year in man-hours lost from work, medical care and mosquito eradication programs. In economic terms this figure represents a 5 per cent tax on all imports into the United States. Malaria causes underdevelopment of large areas in many countries, limiting the food supply and so reducing the economic status as to restrict exports to these countries from the United States.

In this country the principal endemic area lies in the southeastern states, but it has extended as far north as Maine. Mississippi has the highest incidence, followed by South Carolina, Texas and Alabama. Minor endemic areas are present in New Mexico, California, the valley of the lower Sacramento and the Columbia River Valley. Tertian malaria has been almost the sole form encountered; some cases of quartan malaria have been seen, and estivoautumnal malaria has rarely been found.

Extensive antimalaria operations during the past 20 years have eliminated endemic malaria from most cities and towns of the United States, but it continues to be an important medical and public health problem in many rural communities. The general decline in malaria in this country during the past 50 years has been interrupted at fairly regular five to seven-year intervals.[3] Table 1 lists the number of cases contracted within the continental United States during nine years since 1932.[4]

Economic improvement has undoubtedly played an important role in the decrease. The use of insecticides, the deviation of Anopheles mosquitoes from human beings to cattle, the migration of large populations from rural areas in the South to urban centers or other parts of the country and improved antimalaria medication are the main factors

1. Stitt, E. R., and Strong, R. P.: Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1944, pp. 1-18, 58-63 and 119-126.

2. Russell, P.: Epidemiology of Malaria, lecture given at New York University Postgraduate School of Medicine, Nov. 24, 1948.

3. Andrews, J. M.: What's Happening to Malaria in the U. S. A.? Am. J. Pub. Health **38**:931, 1948.

4. Andrews.[3] Monthly Epidemiological Report No. 126, Washington, D. C., Pan American Sanitary Bureau, 1949, p. 20. Hampton, B. C.: Malaria: Numbers of Cases Reported by State Health Officers in 1945 as Compared with Similar Data for Years 1939-44, Pub. Health Rep. **61**:679, 1946. Notifiable Diseases, Year 1947, ibid. **63**:388, 1948. Notifiable Diseases, Third Quarter, 1949, ibid. **64**:1620, 1949.

responsible for the lowered incidence of malaria. There appears to have been no deterioration in the number of mosquitoes or their susceptibility to parasitism.

As World War II dramatically illustrated, malaria is also important from the standpoint of national defense. Approximately 500,000 cases of malaria developed in American troops in the various military areas during that conflict.[5] The major clinical problem was the result of repeated relapses due to P. vivax infections, particularly those originating in the Pacific area. By August 1948 only 10,000 of these 500,000 veterans were continuing to show relapse. In 1947, 190,000 veterans were receiving compensation for malaria. By 1948 this number had fallen to 26,000. These data illustrate two phenomena: (1) the natural course of the disease—unless the patient is again bitten by an infected mosquito, malarial relapses become progressively less frequent with the passage of time and (2) improved administrative procedure—whereas it had previously been a common practice to diagnose and treat malaria on the basis of clinical symptoms alone, in 1948 the Veterans Administration required the demonstration of malarial parasites in a blood smear as an absolute criterion for diagnosis. Clinical observation of a paroxysm is not a reliable basis for the diagnosis of malaria.

TABLE 1.—*Reported Incidence of Malaria in the United States*

Year	Cases	Deaths
1932	68,613	2,540
1933	125,549	4,678
1938	84,296	2,378
1944	45,878	.....
1945	41,671	.....
1946	47,894	.....
1947	17,317	.....
1948 (9 mo.)	8,171	None
1949 (9 mo.)	3,612	None

LIFE CYCLE OF MALARIAL PARASITES

The requirements for spreading malaria are human beings who have sexual forms of the parasites in their peripheral circulation, efficient anopheline hosts and a sustained mean atmospheric temperature above 60 F.[1] Man is the intermediate host of these parasites. They undergo an asexual stage of development (schizogony) in the human red corpuscles; sporozoite → trophozoite → schizont → merocyte → merozoite. Sexual forms, male and female gametocytes, arise from preexisting asexual parasites in the blood at varying intervals. The Anopheles mosquito is the definite host. The parasites go through a sexual stage of development

5. Most, H.: Management of Vivax Malaria in the Veteran, Veterans Administration Technical Bulletin 10-47, Washington, D. C., 1948, pp. 1-9.

(sporogony) in the stomach, body cavity and salivary gland of the mosquito: microgametocyte and macrogametocyte → microgamete and macrogamete → zygote → oocyst → sporoblast → sporozoite. The mosquito suffers no apparent injury from the infection; usually its life is not shortened, nor is its fertility lowered. The duration of the sexual phase in the mosquito varies with the species and the environmental temperature. Once sporozoites develop, a mosquito may remain infectious for three months, since only a portion of the parasites is discharged with each bite.

MOSQUITO ERADICATION

There has been more progress in controlling malaria during the last few years than in the previous 25, due chiefly to the advent of better insecticides. Early attempts to destroy mosquito larvae were disappointing. The methods employed, canalization of streams and oiling of stagnant water, were relatively inefficient and expensive. One gallon (3.78 liters) of DDT in oil will treat the same area of water as 10 to 20 gallons (37.8 to 75.6 liters) of plain oil.[6] This larvicide is not only more economical but more efficient and persistent in its action. Man's eventual conquest of the disease will not depend on better parasiticidal drugs but on complete eradication of the Anopheles mosquitoes. Eradication of anopheline mosquitoes in Brazil was achieved in 1939 and 1940, covering an area of 5,000 square miles (12,950 square kilometers) at an expense of more than $2,000,000.[7] This cost was small compared with the damage which the mosquito had been causing. Many other successful campaigns were carried out in other parts of the world subsequently. Italy expects to eliminate the disease in five years. The island of Cyprus claims to be the first endemic malarial country in the world to have completely rid itself of Anopheles mosquitoes. In the newer methods of control entire reliance is being placed on the use of DDT residual indoor sprays in all houses twice a year. DDT is nonvolatile, and it persists as a fine crystalline deposit for several months. There is little prospect of completely eradicating forest-haunting mosquitoes, particularly in certain areas of Central Africa, but the use of airplane sprays is becoming more prevalent.

Mechanical protection of the individual person relies chiefly on the use of nets and screens (at least 18 meshes to the square inch). Since malarial mosquitoes bite chiefly toward evening, exposure after sunset is dangerous. Houses should be far removed from native habitats. Mosquitoes prefer the lower floors of a house, so that the upper stories are preferable for sleeping. Oil of citronella applied to the skin is often used to keep away mosquitoes, but it is not always effective.

6. Boyd, J. S. K.: Fifty Years of Tropical Medicine, Brit. M. J. **1**:37, 1950.
7. Mosquito Eradication, Editorial, Brit. M. J. **2**:222 1949.

Many types of mosquito traps have been devised in which a mercury vapor lamp is used to attract the insects. Recently, there was reported a method for mosquito destruction which employs mosquito sounds.[8] The calls of wild female anopheline mosquitoes are recorded on a sound machine and replayed on a loud speaker. This serves to bait male mosquitoes of the same species, who are electrocuted by a charged screen placed in front of the speaker.

In the biologic control of mosquitoes the value of shading has long been recognized. Certain natural enemies of the larvae, preferably small fish, may be introduced into swamps, streams, springs and wells. Other natural enemies of the mosquito larvae are protozoan parasites, fungi and certain worms, arthropods and plants.

CHEMOTHERAPY OF MALARIA

The ideal drug for prevention and cure of benign tertian malaria is yet to be discovered. Most authorities advise that use of quinine per se be discontinued, except for cases of cerebral malaria in which quinine, given intravenously, is the drug of choice. Quinacrine hydrochloride (atabrine® dihydrochloride) is likely to be superseded by more recently discovered antimalarial drugs, although there is no doubt that its use as a suppressant had a vital influence on the course of the Southwest Pacific campaigns during World War II. Fairley stated that chloroquine phosphate is probably the most potent schizontocide yet discovered.[9] It is valuable as a suppressant given once weekly and in the intensive treatment of clinical attacks. Chlorguanide (paludrine®) hydrochloride is probably equally effective in suppressing clinical malaria, in once weekly dosage, although this British product has yielded drug-resistant variants of the parasite. Monk was of the opinion that pamaquine (plasmochin®) naphthoate is of the greatest value in eliminating vivax infections and reducing the relapse rate, and he stated that this drug is less toxic than generally believed.[10] The effect of the drug is enhanced when it is combined with quinine or chlorguanide hydrochloride. For the radical cure of P. vivax malaria pentaquine and iso-pentaquine are now becoming available. More time and experience are needed to decide whether they are superior to combined pamaquine and quinine therapy. During military operations it is advisable to have at least two antimalarial drugs for suppressive or prophylactic purposes, since specific resistance may develop to any particular one.

8. Kahn, M. C., and Offenhauser, W.: The First Field Tests of Recorded Mosquito Sounds Used for Mosquito Destruction, Am. J. Trop. Med. **29**:811, 1949.

9. Fairley, N. H.: Malaria: Chemotherapy, Brit. M. J. **2**:891, 1949.

10. Monk, J. F.: Modern Therapy of Benign Tertian Malaria. Brit. M. J. **1**:1221, 1948.

IMMUNITY

In man there is considerable evidence to show that immunity in malarial districts may be acquired from repeated and persistent infections in childhood. In heavily endemic areas different surveys have shown that over 90 per cent of the young children have malarial parasites in their blood, while the rate of infection among the adults is usually much lower.[1] Many of these children have evidently acquired a tolerance to the infection and go about playing without any acute symptoms of the disease. It has been suggested that newly born infants have a temporary immunity, acquired in utero as a result of stimulation by toxins absorbed from the maternal circulation. Resistance to malaria develops in connection with proliferation and increased activity of the reticuloendothelial cells, especially in the spleen, but also in the liver and bone marrow. These engulf and destroy the infected red blood cells, as well as the free parasites. This stimulation may represent a hypersensitive reaction to the foreign protein of the parasite, since it disappears when the plasmodia are completely eliminated. This immunity disappears under adverse conditions, such as shock, exhaustion, trauma, change of climate or alcoholic excesses. Attempts have been made to demonstrate the presence of specific antibodies in the host, with conflicting results.

Yount and Coggeshall recently reported on the inoculation of 21 volunteers at a state prison with sporozoites of P. vivax (Southwest Pacific Chesson strain).[11] None of these prisoners had had malaria previously. Some were "cured" after their initial attack with 60 mg. of pentaquine and 2 Gm. of quinine given daily for two weeks. Others were allowed to have several relapses, following which they were "cured" with the same therapy. After varying intervals, these volunteers were reinoculated with sporozoites and trophozoites of both homologous and heterologous strains. Those reinfected with the homologous organisms immediately after the clinical "cure" did not acquire malaria. Reinfection with the Chesson strain some nine months later, however, produced clinical malaria. There was no evidence of cross immunity. Those volunteers given reinjections of heterologous strains immediately after the completion of pentaquine and quinine therapy did acquire malaria. This study indicates that we have little reason to hope for an effective vaccine against malaria. Resistance to malaria depends on active infection, either clinical or subclinical. After eradication of acute or chronic vivax malaria by chemotherapy, there exists a temporary immunity to reinfection by the homologous organism, lasting up to two months with

11. Yount, E. H., and Coggeshall, L. T.: Status of Immunity Following Cure of Recurrent Vivax Malaria, Am. J. Trop. Med. **29**:701, 1949.

trophozoite inoculation and up to 13½ months with sporozoite inoculation. The immune reaction is proportional to the number of relapses, but not to the duration of infection prior to cure.

LATENCY AND RELAPSE PHENOMENA

The latency and relapse patterns of malarial infections vary with the type and geographic origin of the specific parasites. P. falciparum infections produce little morbidity and practically no mortality, with the proper use of quinacrine. Administration of this drug results in definitive cure of these infections. Latency, on the other hand, is best exemplified in quartan malaria. P. malariae may be harbored for extremely long periods without symptoms and are often transmitted unknowingly by transfusions given years after the original infection. Relapses are common.

Pacific vivax malaria produces frequent continuous relapses in 80 per cent of cases, with a mean latent interval of 42 days after treatment is discontinued.[5] Suppressive therapy modifies the relapse pattern, and some Pacific strains have been reported with latent intervals of 18 to 24 months. Since 20 per cent of vivax infections are cured with each relapse, it would be a matter of two to three years until only 1 per cent of those originally infected were eligible for subsequent attacks. Mediterranean strains of vivax malaria have a characteristically long latent period, usually nine months or more, with only a 30 per cent relapse rate. The St. Elizabeth strain of P. vivax, commonly used for inducing malaria in the therapy of syphilis of the central nervous system, has a latent period of nine to eleven months and a relapse rate of only 2 per cent.

TISSUE PHASES OF MALARIA (PREERYTHROCYTIC AND EXOERYTHROCYTIC FORMS)

In 1934 the tissue stage of avian malaria was demonstrated in the reticuloendothelial system of birds.[12] It was not until 1948, however, that Shortt and his colleagues established the tissue phase of mammalian malaria.[13] This discovery was extremely significant from the parasitological, clinical and chemotherapeutic viewpoints. These workers infected a monkey with Plasmodium cynomolgi and killed the animal seven days later. Preerythrocytic forms of P. cynomolgi were observed in the parenchymal cells of the liver and in no other viscus. The discovery suggested that if this cycle persisted after establishment of the blood infection it might play an important role in maintaining the malar-

12. Fairley, N. H.: Malaria: Life Cycle, Brit. M. J. **2**:825, 1949.

13. Shortt, H. E.; Garnham, P. C. C., and Malamos, B.: The Pre-Erythrocytic Stage of Mammalian Malaria, Brit. M. J. **1**:192, 1948.

ial infection over long periods and in producing relapses. Later that same year, it was proved by Shortt and Garnham that a late tissue stage occurs in P. cynomolgi malaria.[14] They demonstrated exoerythrocytic parasites in the liver of a monkey that had been infected 103 days previously, by which time the disease was latent and the schizonts had temporarily disappeared from the peripheral blood.

Unfortunately, there is no suitable laboratory animal that can be experimentally infected with any of the human species of malarial parasites. This difficulty was overcome in 1948, when Shortt and his colleagues used a volunteer to demonstrate that a tissue phase of P. vivax malaria existed in man.[15] Seven days after infection liver biopsy was performed through a laparotomy wound, and sections revealed plasmodial masses in the parenchymal cells. It is evident that vivax sporozoites rapidly gain access to the blood after being inoculated by mosquitoes but soon leave the circulation and invade the parenchymal cells of the liver. Here they pass through a developmental cycle lasting at least eight days, at which time the mature schizonts rupture, allowing merozoites to enter the circulation and cause a subclinical parasitemia for several days. This cycle repeats itself until a sufficient degree of parasitemia is achieved to produce clinical symptoms.

In 1949 Shortt and his colleagues demonstrated that a tissue phase exists in human falciparum malaria.[16] They allowed infected mosquitoes to feed on a volunteer during three successive days. Six days after the initial exposure liver biopsy was done via laparotomy, and sections revealed three stages of preerythrocytic schizonts in the parenchymal cells. The preerythrocytic forms of all three species, P. cynomolgi, P. vivax and P. falciparum, are closely similar morphologically.

In quartan malaria due to P. malariae the sporogenous and erythrocytic cycles proceed slowly. Nothing is known of the tissue cycle in this type of malaria, but the long latent periods, the presence of late relapses, the difficulty of obtaining complete cure and the accidental transmission of quartan malaria by blood transfusion in instances in which the donor has been away from malarial areas for many years without symptoms, all suggest that an exoerythrocytic phase may persist for a long time.

To summarize and fit all these new pieces of knowledge together, it seems that P. vivax and P. falciparum exist in five distinct forms:

14. Shortt, H. E., and Garnham, P. C. C.: Demonstration of a Persisting Exo-Erythrocytic Cycle in Plasmodium Cynomolgi and Its Bearing on the Production of Relapses, Brit. M. J. **1**:1225, 1948.

15. Shortt, H. E.; Garnham, P. C. C.; Covell, G., and Shute, P. G.: The Pre-Erythrocytic Stage of Human Malaria, Plasmodium Vivax, Brit. M. J. **1**:547, 1948.

16. Shortt, H. E.; Fairley, N. H.; Covell, G.; Shute, P. G., and Garnham, P. C. C.: The Pre-Erythrocytic Stage of Plasmodium Falciparum, Brit. M. J. **2**:1006, 1949.

(1) the sporozoite, (2) the preerythrocytic form in the liver, (3) the schizont in the red corpuscles, (4) the exoerythrocytic form in the liver and (5) the gametocyte in the red blood cells. Merozoites released by the liver may enter the red corpuscles to produce clinical malaria or return to the hepatic cells and repeat the process of exoerythrocytic schizogony indefinitely. This recently acquired information readily explains the phenomena of latency and relapse. Apparently the exoerythrocytic parasites, because of their habitat within the liver parenchyma, are protected from the host's immune mechanism and only become susceptible to antibodies when merozoites are released from the liver. Those merozoites which reenter other hepatic cells are similarly protected, and the hepatic cycle can go on indefinitely, entirely independent of the blood infection. A person's immunity is purchased only at the expense of clinical activity. P. falciparum apparently does not

TABLE 2.—*Geographic Source and Type of Malaria in 510 Admissions*

Plasmodium Vivax Malaria		
Pacific		460
Europe and Mediterranean	25	
China-Burma-India	16	
Central America	3	48
United States	2	
Mediterranean and China-Burma-India	1	
Europe and Central America	1	
		508
Plasmodium Malariae Malaria		
Pacific		1
Europe		1
		2

develop the exoerythrocytic, or late tissue, phase but is otherwise similar. It remains to be determined, however, why P. vivax is so much more difficult to eradicate from the tissues than P. falciparum. Another phenomenon which remains unexplained is the different therapeutic response to antimalarial drugs in blood-inoculated and mosquito-transmitted vivax malaria.

CLINICAL DATA

A survey has been conducted of admissions for malaria to the Veterans Administration Hospital, Aspinwall, Pa., from January 1944 to December 1949, inclusive. This study was not planned in advance, and the assembled clinical data represent the observations of many physicians and technicians on the staff of this hospital. During this six year period there were 728 admissions to the hospital in which a diagnosis of malaria was given. For 218 of these the diagnosis was made only on clinical grounds, usually based on several of the following criteria: history of malaria or residence in endemic malarial region, chills, fever, aches, gastrointestinal symptoms, splenomegaly, anemia, false positive serologic

blood reactions and/or clinical improvement following the administration of antimalarial drugs prior to entering the hospital. In many instances epinephrine was administered subcutaneously in an effort to produce parasitemia, but this was successful on only one occasion. For purposes of analysis these 218 admissions were excluded from our study, leaving a total of 510 admissions in which the clinical diagnosis was confirmed by the finding of malarial parasites in the peripheral blood. These 510 admissions represented 475 World War II veterans, of whom 33 had two admissions and one had three admissions. Of these, 323 gave a history of having had malaria during military service. The geographic source and type of malaria are listed in table 2.

The number of admissions per month began with two in January 1944, rose gradually to a peak of 57 in January 1946 and declined slowly until

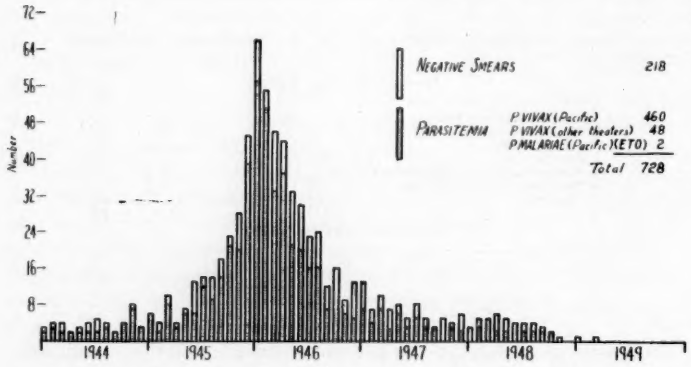

Fig. 1.—Monthly admissions to Aspinwall, Pa., Veterans Administration Hospital from January 1944 to December 1949.

October 1948 (fig. 1). No case of malaria with parasitemia has been encountered at our hospital from November 1948 to the time of the present writing, a period of 18 months. Admissions per year were as follows:

Year	No. Admissions
1944	33
1945	146
1946	276
1947	44
1948	11
1949	0

A crude correlation was attempted between these data and the number of veterans receiving compensation for malaria through the Pittsburgh Regional Office of the Veterans Administration. This office

serves 27 counties in western Pennsylvania and four counties in northern West Virginia. The total veteran population of these 31 counties is 514,800. In 1946 more than 3,000 of these veterans were receiving compensation for malaria. By June 1949 there were only 600 awards for "recurrent disabilities and residuals of malaria." In December 1949 there were 56, and by Jan. 31, 1950 the number had fallen to 33 awards for malaria.

Another crude correlation was attempted between the rate of admissions for malaria to our hospital and the number of monthly discharges of Army and Air Force personnel during the same six year period from

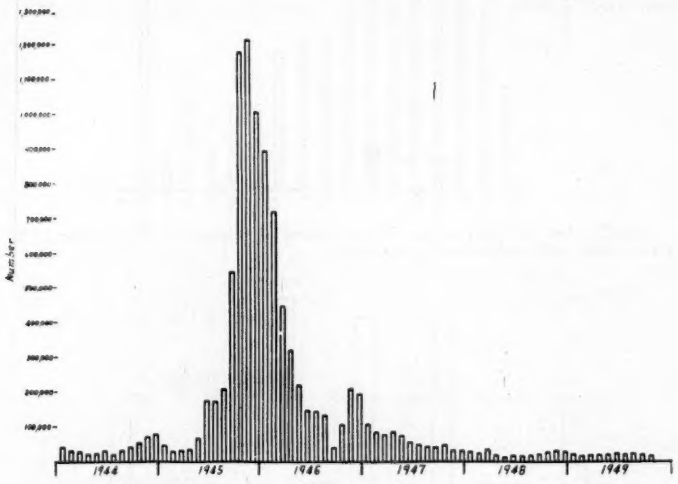

Fig. 2.—Monthly discharges of Army and Air Force personnel in the United States from January 1944 to December 1949 (courtesy of the Adjutant General, Department of the Army).

January 1944 to December 1949 (fig. 2). These data were supplied through the courtesy of the Adjutant General, Department of the Army, and included figures for Air Force personnel prior to January 1948. In January 1944 there were 38,336 discharges from military service; the peak was reached in November 1945, with 1,205,048 discharges, and in October 1949, only 13,137 were returned to civilian life. It can be seen that the curves in figures 1 and 2 are similar, with a two to three month lag between their peaks. Similar data concerning Navy, Marine Corps and Coast Guard personnel were not obtained.

As mentioned previously, all the 510 admissions for malaria with parasitemia were of veterans of World War II. Their ages varied between 20 and 44 years (fig. 3), the average age being 24 years.

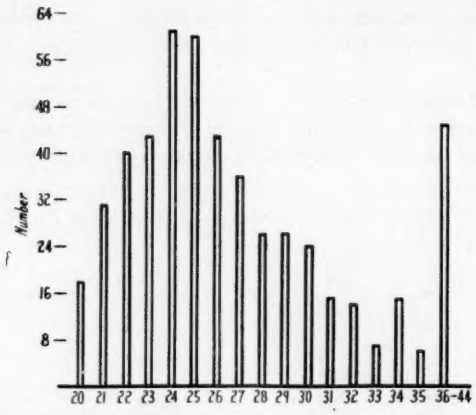

Fig. 3.—Age incidence among 510 admissions of veterans of World War II to the hospital with malaria and parasitemia.

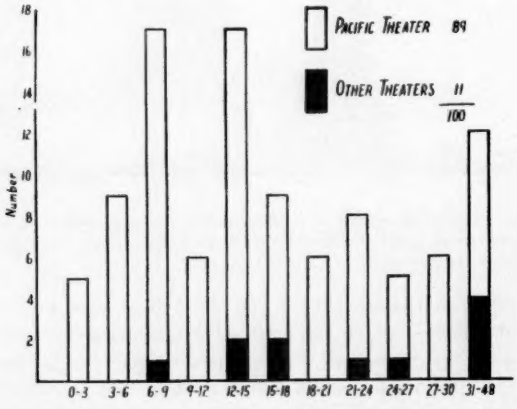

Fig. 4.—Minimum known duration of malaria in months among 100 admissions for P. vivax malaria.

In 100 of the 508 admissions for vivax malaria the minimum known duration of disease could be ascertained from the date of the first known malarial attack to the time of entry into our hospital (fig. 4). The

average was 6.1 months. In 11 patients the malarial infestation was known to have existed for more than 30 months, and two of these had the disease for at least 46 and 48 months, respectively. Several of these 11 patients claimed to have had 20 to 25 "attacks of malaria" during this period.

In 168 patients with vivax malaria there had been no previous clinical attacks. Many of these veterans gave a history of receiving suppressive therapy during military service. One hundred and fifty-seven served in the Pacific theater and 11 in other areas. An attempt was made to estimate the number of malarial attacks in the remaining patients, based entirely on history. These figures obviously would be subject to inaccuracies, since many of the so-called attacks of malaria could well

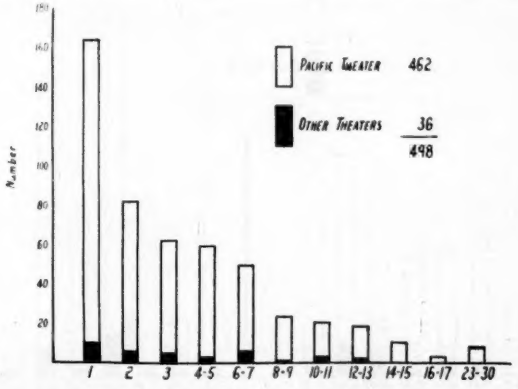

Fig. 5.—Approximate latent period in months between recurrence of P. vivax malaria (498 admissions) as estimated from date of discharge from service or known previous attack.

have been one of several acute infectious diseases. More than half the patients stated they had had between two and five attacks, and over 20 alleged to have had more than 10 attacks of "malaria."

The approximate latent period between recurrences of vivax malaria is shown in figure 5. This was estimated from the time of discharge from military service, when suppressive therapy was discontinued, or from the time of a known previous attack which was substantiated at our hospital or at the Pittsburgh Regional Office of the Veterans Administration. The average was 4.2 months. Seven patients had latent periods of from 24 to 30 months, during which time no antimalarial drugs were being taken.

The highest temperatures and pulse rates at the time of admission, or at the time of a malarial exacerbation during hospitalization, are recorded in figure 6. In more than 30 admissions the temperature was normal throughout hospitalization, despite an established parasitemia; antimalarial drugs had been administered to all these patients promptly. In no instance was any specific therapy administered until parasites were demonstrated in the blood. The average temperature was 102.2 F. Traditionally, malaria is accompanied with a relative bradycardia. The patients in almost half our 508 admissions, however, had a pulse rate in excess of 110 per minute. At the time the temperature reached its highest peak, the average pulse rate was 111 per minute.

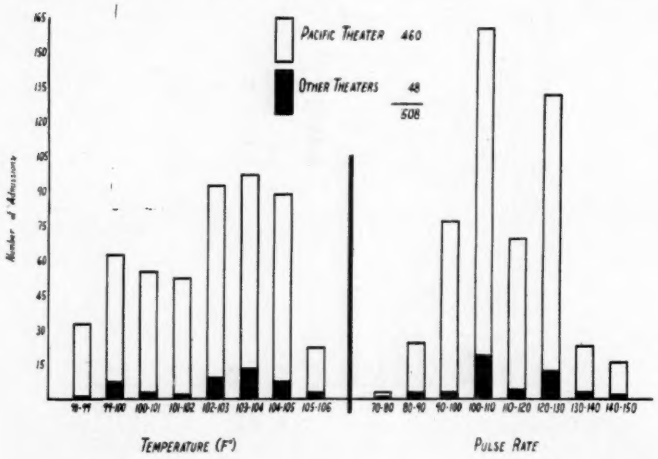

Fig. 6.—Highest temperature and pulse rates at time of admission or during exacerbation in hospital in 508 admissions for P. vivax malaria.

In figure 7 are recorded the lowest red blood cell counts and the highest white blood cell counts at the time vivax parasitemia was demonstrated. In 27 admissions there were less than 3,000,000 erythrocytes per cubic millimeter. The average erythrocyte count was 4,400,000. In 97 admissions the white blood cell count was below 5,000 per cubic millimeters, and in 30 it exceeded 10,000. The average leukocyte count was 6,470.

Figure 8 lists the other clinical and laboratory findings in these 508 admissions for P. vivax malaria. In all cases there was a history of fever prior to or shortly after entrance to the hospital, and this symptom is

not listed in the chart. Chills occurred in 499 instances. The next commonest symptom was generalized aching (myalgia, cephalalgia or both). In 40 per cent one or more of the following gastrointestinal symptoms appeared, listed in order of frequency: vomiting, nausea, abdominal pain, diarrhea.

Splenomegaly was recorded in 41 per cent of the admissions. This figure is obviously low because the findings are based on the examinations of different observers at infrequent intervals. It has been shown that frequent abdominal examinations of patients with active malaria will result in a spleen index as high as 90 per cent. Nevertheless, a correlation was attempted between the single finding of splenomegaly and the other

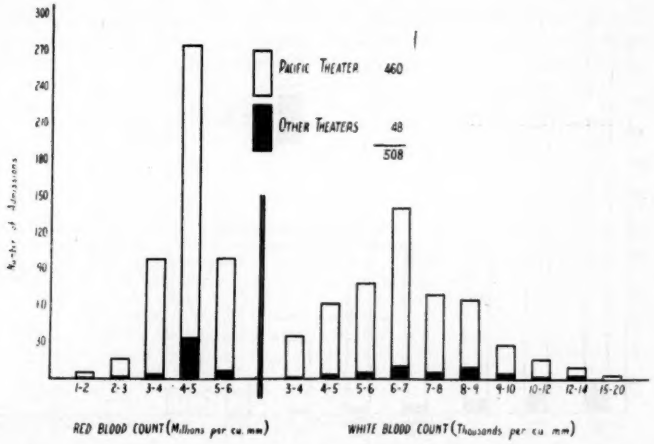

Fig. 7.—Lowest red blood cell counts and highest white blood cell counts in 508 admissions for P. vivax malaria.

clinical and laboratory data. No significant differences were noted between this group of 202 admissions and the entire group of 508, except that hepatomegaly was commoner in patients with enlarged spleen (7 per cent) than in those in whom the spleen was not palpated (1.5 per cent).

In about 30 per cent of the admissions a positive serologic reaction was obtained in the blood to Kahn, Wassermann and/or cardiolipin tests. In most instances these were proved to be false positive or biologic reactions during the course of hospitalization or on subsequent admissions. All other patients were referred to their family physicians or local clinics for follow-up serologic examinations.

Listed in the order of frequency, other findings were albumin and/or casts in the urine, herpes simplex, respiratory symptoms (cough, coryza,

and/or pharyngitis), hepatomegaly, central nervous system symptoms (delirium, meningismus, vertigo, neuropathy or coma) and urticaria.

Two patients had quartan malaria with P. malariae parasitemia. One veteran served in the Southwest Pacific and the other in the European theater of operations. Their maximum temperatures were 104.8 and 102 F., and their highest pulse rates were 132 and 104 per minute, respectively. The first patient had a palpable spleen, with leukopenia (4,800 cells per cubic millimeter). The disease in both patients responded promptly to quinacrine therapy.

In table 3 are listed some of the associated clinical data in our group of admissions for malaria. One patient with infectious hepatitis and one

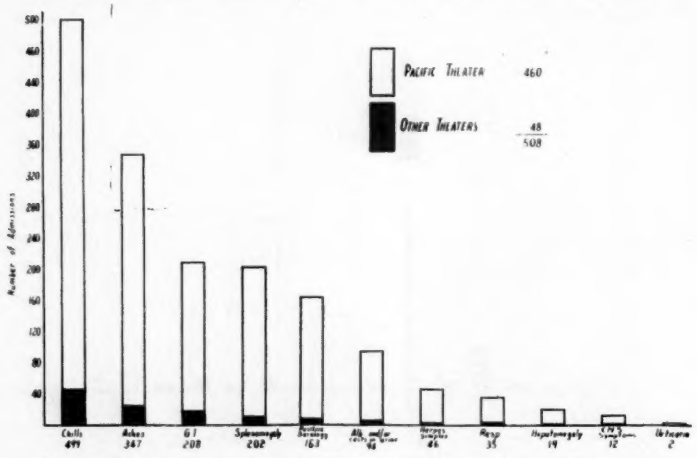

Fig. 8.—Other clinical and laboratory data in 508 admissions to the hospital for P. vivax malaria.

with amebic hepatitis are included among the 19 with hepatomegaly. There were two deaths in the entire group (neither patient was autopsied). One patient, who had had chronic atrophic lichen planus for five months, had been taking quinacrine prior to his admission to the hospital. Administration of the drug was continued in the hospital because of persistent parasitemia. Later pancytopenia and an exacerbation of the dermatitis developed, at which time quinacrine treatment was stopped. The patient died of a cerebral hemorrhage nine weeks after his admission. The second death was in a veteran who had been operated on for ruptured malarial spleen, with recovery. He was readmitted to the hospital 3½ months later for active malaria. Clinical symptoms subsided, and parasitemia disappeared following quinacrine therapy on both

occasions. Nine days after the second discharge the patient reentered the hospital in a state of delirium, with dyspnea, cyanosis, vomiting, dehydration and peripheral circulatory failure. Blood smears showed numerous vivax plasmodia. Administration of 3 grains (0.19 Gm.) of quinacrine hydrochloride intramuscularly every third hour and an intravenous infusion of quinine bisulfate (10 grains [0.65 Gm.] in 1,000 cc. of sodium chloride solution) were ordered, but the patient died two hours following admission, after only one dose of quinacrine was given. Experiments in monkeys have shown that splenectomy greatly increases their susceptibility to malaria, and clinical observations have borne this out in human beings.

TABLE 3.—*Associated Clinical Data in 508 Admissions for P. Vivax Malaria*

	Number
Amebiasis	9
Admitted for pneumonia	5
Clinical jaundice	5
Ancylostomiasis	4
Transfusions	3
Peripheral neuritis	2
Ascariasis	1
Infectious hepatitis	1
Amebic hepatitis (included in amebiasis)	1
Quinacrine lichen planus and pancytopenia (death)	1
Ruptured spleen (death on readmission)	1
Retinal hemorrhages	1
Toxic erythema	1
Admitted for subacute bacterial endocarditis	1
Admitted for intracranial lesion	1

Listed below are the number of patients to whom the antimalarial drugs were administered, all in the accepted dosages:

Drug	No. of Patients
Quinacrine	458
Chloroquine	32
Quinine	28

In four instances quinacrine was administered intramuscularly because of the patient's inability to take oral medication (coma, vomiting, etc). In 10 patients quinacrine was combined with chloroquine or quinine because of poor response to one of the drugs or severity of the illness. The two deaths have been mentioned previously. In all the remaining cases there was a satisfactory response to therapy. In one patient, chills and fever disappeared with quinacrine administration but parasitemia continued for nine days. In many cases with parasitemia antimalarial therapy had been started prior to admission to the hospital. This undoubtedly modified some of the clinical findings, particularly the temperature and pulse rate.

COMMENT

In July 1944 a mosquito survey was conducted by the United States Public Health Service at the Aspinwall Veterans Hospital and within a 1 mile (1.6 kilometer) surrounding zone. No larval or adult forms of Anopheles quadrimaculatus were found. Our clinical survey demonstrates the self-limited nature of vivax malaria and the termination of malaria as a medical problem in veterans of World War II who now reside in regions where there are no suitable definitive hosts to propagate the disease. Our hospital admissions for malaria declined in proportion to the reduction in the number of servicemen demobilized. We observed only 11 patients who were having malarial paroxysms more than 30 months after the onset of the disease. This coincides with the experience of Hill and Amatuzio.[17] They reported the clinical disease terminated at the end of one year in 24.5 per cent, at the end of two years in 52.9 per cent and at the end of three years in 18.3 per cent; only 4.3 per cent of their patients were having attacks in the fourth year.

The recent experience of many observers has emphasized the importance of the basic pattern of myalgia, chills and cyclic fever in the symptomatology of malaria. In our survey these were by far the most frequent symptoms. Attention is called, however, to the protean manifestations of the disease. Gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal pain) were present in 41 per cent of the admissions. Respiratory symptoms (cough, rhinitis, sore throat, bronchitis, pain in the chest) were present in 7 per cent, and central nervous system manifestations (coma, delirium, meningismus, neuropathy) were observed in 2 per cent. Other observers have commented on these less recognized symptoms. Hill and Amatuzio reported gastrointestinal symptoms in 18.8 per cent, central nervous system symptoms in 11 per cent and respiratory symptoms in 4 per cent.[17] Most and Hayman discussed these relatively uncommon clinical manifestations of malaria and warned against the pitfalls of misinterpreting symptoms simulating acute abdominal conditions and acute respiratory disease.[18] They also noted the not infrequent association of central nervous system symptoms and pointed out that their occurrence does not of necessity mean "cerebral malaria." We had no case of proved cerebral malaria in the present series.

Hyman observed 100 patients with proved malaria whose conditions were misdiagnosed as other diseases. Of these, 34 per cent were thought to have disease of the heart and lungs, 26 per cent disease of the

17. Hill, E., and Amatuzio, D. S.: Southwest Pacific Vivax Malaria: Clinical Features and Observations Concerning Duration of Clinical Activity, Am. J. Trop. Med. **29**:203, 1949.

18. Most, H., and Hayman, J. M., Jr.: Uncommon Clinical Manifestations of Vivax Malaria, J. A. M. A. **130**:480, (Feb. 23) 1946.

abdomen, 21 per cent disease of the musculoskeletal system, 12 per cent disease of the head, 4 per cent disease of the kidney and 3 per cent other miscellaneous diseases.[19]

We detected splenomegaly in 40 per cent and hepatomegaly in 3.7 per cent of the admissions. Hill and Amatuzio reported splenomegaly in 27.6 per cent and hepatomegaly in 15.1 per cent. Bianco and his associates recorded splenomegaly in 47 per cent and made no mention of hepatomegaly.[20] Kern and Norris, in a planned study, noted splenomegaly in 85 per cent and hepatomegaly in 60 per cent of more than 1,000 cases.[21] The last study illustrates the value of repeated planned examinations by more than one observer.

We noted herpes simplex in 9 per cent of our admissions and urticaria in 0.4 per cent. Bianco and his co-workers reported herpes in 19.5 per cent and urticaria in 0.4 per cent. A positive blood serologic reaction was observed in 32 per cent of our admissions. Bianco and his collaborators observed that 21 per cent of their patients had a positive Kahn reaction within the first two weeks of illness. We observed no cases of so-called blackwater fever. However, in 18 per cent of the admissions some degree of albuminuria, hematuria or cylindruria was present.

Metcalf and Ungar noted the average white blood cell count to be 6,336 per cubic millimeter.[22] Hill and Amatuzio reported the white blood cell count to be less than 5,000 per cubic millimeter in 24.3 per cent, and Bianco and his associates found white blood counts below 5,000 per cubic millimeter in 15.4 per cent. In our survey, the average white blood cell count was 6,470 per cubic millimeter and 19 per cent were below 5,000.

SUMMARY

The high incidence, morbidity and mortality of malaria make this a disease of world-wide medical, economic and military importance. Malaria has declined fairly steadily in the United States during the past 50 years. The control of malaria has made great strides in recent years, owing chiefly to better insecticides, and also to the discovery of effective parasiticidal drugs. Active immunity to malaria is transient and specific for homologous strains of plasmodia. Latency and relapse patterns of

19. Hyman, A. S.: Clinical Masquerades of Malaria, U. S. Nav. M. Bull. **45**: 287, 1945.

20. Bianco, A. A.; Saunders, J. M.; Levine, A. S., and Cohen, R.: Long-Term Observation of Plasmodium Vivax Malaria in the Returned Serviceman, U. S. Nav. M. Bull. **47**:352, 1947.

21. Kern, R. A., and Norris, R. F.: Liver Involvement in Malaria, U. S. Nav. M. Bull. **43**:847, 1944.

22. Metcalf, R. J., and Ungar, J.: Relapsing Malaria, U. S. Nav. M. Bull. **43**:859, 1944.

malarial infections vary with the type and geographic origin of the parasites. The recent discovery of the tissue phase of human malaria in parenchymal liver cells readily explains these phenomena.

From January 1944 to December 1949, inclusive, there were 510 admissions to the Veterans Administration Hospital, Aspinwall, Pa., for proved malaria. The epidemiological aspects, clinical and laboratory findings and response to antimalarial therapy are reviewed.

The above data correspond fairly well with other studies reported in the literature.

CONCLUSIONS

In the absence of suitable Anopheles mosquitoes to propagate the infection by reinoculation, vivax malaria is a self-limited disease. Because of the sparsity of these definitive hosts in this area, malaria does not appear to be a serious postwar problem in Western Pennsylvania.

ALTERATIONS IN RENAL FUNCTION, INCLUDING HEMATURIA, IN MAN DURING INTRACRANIAL AIR STUDIES

Alterations in Cardiac Function

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LOS ANGELES

THE QUESTION of the relationship between the central nervous system and the kidney is of great significance and involves not only somatic vasomotor and endocrine shifts in water balance [1] but possibilities in nephritis as well. In previous experiments on the unanesthetized dog, purely central nervous stimuli, osmotic, alkaloidal and hormonal, were shown [2] to produce drastic alterations in renal function, including albuminuria and hematuria. The clinical experiments hereafter detailed attempt primarily to demonstrate whether analogous changes occur in man following a purely central nervous stimulus.

The evidence for direct relationship between brain and heart has been previously summarized,[3] and electrocardiographic changes after pneumoencephalography have been demonstrated.[4] In our patients

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Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Pick, E. P.: The Regulation of Water Metabolism, in Harvey Lectures, 1929-1930, Baltimore, Williams & Wilkins Company, 1931, p. 25. (*b*) Fulton, J. F.: Physiology of the Nervous System, ed. 3, New York, Oxford University Press, 1950, p. 422.

2. Weinberg, S. J., and Marx, H.: Untersuchungen zur Diurese, Arch. f. exper. Path. u. Pharmakol. **176**:291, 1934.

3. Weinberg, S. J.: Cardiac Arrhythmias of Central Origin, Ann. West. Med. & Surg. **2**:83, 1948.

4. (*a*) Abeles, M. M., and Schneider, D. E.: Electrocardiographic Changes During Encephalography (20 Cases), Am. J. M. Sc. **190**:673, 1935. (*b*) Bick, M. W., and Epstein, B. S.: Electrocardiographic Changes During Pneumoencephalography, Am. Heart J. **26**:200, 1943.

studied by ventriculography and pneumoencephalography electrocardiographic analyses were coincidentally obtained.

The occasional occurrence of an oliguria following ventriculography and encephalography leads one to believe that a direct relationship may exist between central nervous stimulation and total suppression of renal output. With this additional possibility in mind, a series of studies was performed on patients routinely scheduled for ventriculograms and pneumoencephalograms.

PROCEDURE

In 13 male patients at Brentwood Neuropsychiatric Hospital a control diuresis was induced on the day before the air study was to be performed. Urine specimens were collected at 30 minute intervals by means of an indwelling catheter. One quart (0.9 liter) of weak tea (or water, if tea was considered unpalatable) was followed by additional quantities spaced so as to maintain a state of diuresis in the patient for approximately three hours. A sample of venous blood was taken for urea nitrogen analyses. The volume intake and time of output were used as a guide for the day of the air transfer in order that a satisfactory diuresis would be in progress when the neurosurgeon was ready to perform the transfer. Control curves were thus obtained showing the response of each person to the simple procedure of drinking a quantity of water and being catheterized. When ventriculograms were to be made, the trephination was done prior to the control diuresis procedure.

On the day of the air transfer the patient was given a quantity of fluid to drink equal to that in the control study, generally about 2 quarts (1.8 liters). Timed catheterized urine specimens were collected. When the diuresis had been in progress for at least 30 minutes and a blood specimen had been taken, the electrocardiographic leads were attached. The air transfer was then performed immediately, with electrocardiographic recording during the transfer and for one to two minutes thereafter. At this point the bladder was again emptied and the patient taken to the roentgenographic department. After the roentgenograms were completed, the patient was returned to the ward, and urine specimens were collected at 30 minute intervals until the diuresis had returned. For some patients it was necessary to combine two concurrent specimens in order to obtain enough urine for accurate analysis. A blood specimen was taken during the antidiuretic phase.

All urine specimens were examined for volume, urea nitrogen, chloride, specific gravity, qualitative reactions for sugar and albumin and microscopic formed elements.

The observations on renal output were reported as follows: volume in cubic centimeters per minute and chloride and urea nitrogen in milligrams per minute; the specific gravity was indicated as thousandths above 1.000; that is, a specific gravity of 1.012 was plotted as 12. Red blood cells, when present, were estimated as the number per high power field. Qualitative sugar and albumin determinations were done on all urine specimens.

In observations of this type, in which the water output may change in a short time from a large volume to as little as one-fiftieth or less, it would be misleading to report the chloride or urea nitrogen elimination in terms of their concentration in the samples. The concentration by definition is the amount per volume, and, when the aqueous volume is the principal variable, the concentration figures reflect only changes in the water output. By reporting each of their components, i. e., the

volume per minute (approximately the water [H_2O] output) and the chloride and urea nitrogen in milligrams per minute, it was considered that a more accurate representation was being given of the quantitative function of the kidney.

Of the total of 13 subjects studied, two were observed during both ventriculography and pneumoencephalography. Three patients were dropped from the study, leaving 10 subjects, with a total of 12 complete studies. Of the three dropped, one vomited excessively just after the air transfer, resulting in uncertainty concerning the volume intake and state of hydration. One subject produced no diuresis after consuming 2 quarts of tea on the trial day before the air transfer. The third patient failed to have a diuresis. These last two were considered poor subjects for this study. All the men were patients in the Brentwood Neuropsychiatric Hospital and, therefore, may be considered possibly to have labile emotional systems. Perhaps the "emotional kidney function mechanism" of these two had already become effective prior to the air transfer.

Of 10 subjects used in this paper, four had ventriculograms, four had pneumoencephalograms and two had both. In general, the pneumoencephalographic procedure produced the more pronounced antidiuretic effect. This was particularly evident in the two patients on whom both procedures were done several months apart. (In one subject the ventriculogram was made first, whereas in the second the pneumoencephalogram was first.)

RESULTS

The following changes were observed, although not all of them appeared in all the subjects: (1) electrocardiographic alterations, including one instance of cardiac arrest, (2) decrease in water, chloride and urea nitrogen output of the kidney for varying lengths of time, followed by return of diuresis, (3) appearance of red and white blood cells in the urine, (4) appearance of albumin in the urine (one case) and (5) an increase in epithelial cells in the urine. Figures 1, 2, 3 and 5 illustrate changes that were observed. Figure 1 is almost a complete prototype, lacking only the appearance of albumin in the urine.

The first urine sample noted in figure 1 was collected at onset of diuresis. The next three specimens were taken during the diuresis before the air transfer was performed, and the next sample following was obtained shortly after the air transfer. The remainder were taken after the patient's return from the x-ray department. The antidiuretic phase, with a concomitant drop in chloride and urea nitrogen and a rise in specific gravity, persisted for five hours, followed by a return of the diuresis. Red and white blood cells began to appear in the urine approximately one hour after the air injection. They had been noted in other patients of the series as early as one-half hour after the transfer and attained a peak before the end of the antidiuretic phase. One subject exhibited hematuria on the following day, but there was no certainty that this was of renal origin, and it may have resulted from trauma produced in some other manner. The possibility of trauma from the catheterization can be eliminated, as no red cells were observed for three

hours after catheterization. Figure 2 was reproduced from a previous publication by one of us,[2] illustrating renal functional alterations following injection of 20 per cent sodium chloride solution into the cerebral ventricles of an unanesthetized dog. The graph is included to show the similarity of this response to that of patient M. K. (fig. 1).

Figure 3 illustrates data on another patient with pneumoencephalography, in whom traces of albumin appeared 1½ hours after the air transfer, along with numerous red blood cells. Unfortunately, the return

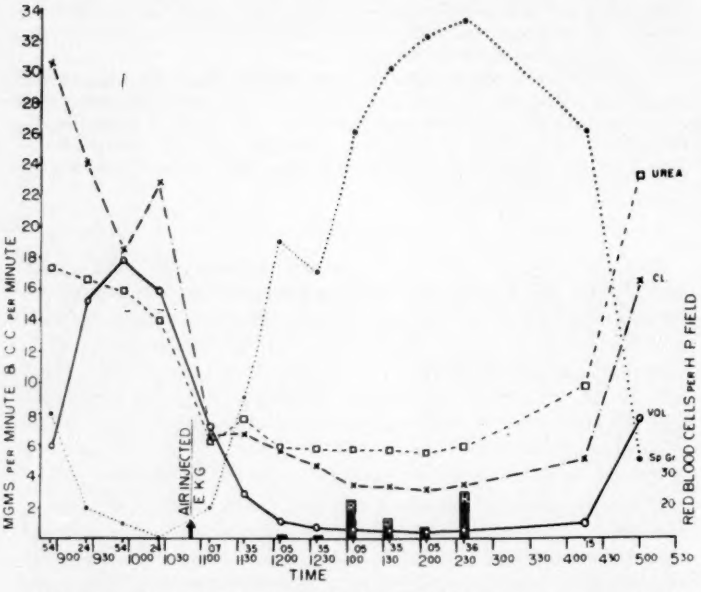

Fig. 1 (patient M. F.).—Urinary volume, chloride, urea nitrogen and red blood cell output after routine pneumoencephalography in man.

of the diuresis was either not pronounced or not followed long enough, and the chemical analysis of the last two specimens was incomplete.

Figure 4 shows the response during ventriculographic study in which the same changes were noted but were of shorter duration and perhaps not so severe. It may be seen that the chloride and urea nitrogen output increased before the increase in water output occurred. This type of phenomenon was noted in varying degrees and combinations in eight of the 12 studies. An extreme example of this type of variance is shown in figure 5 (pneumoencephalogram). This patient was the only subject

in whom the urea nitrogen output increased during the antidiuretic period; in the remaining 10 the drop occurred along with the decrease in water output, but the urea, and in some cases the chloride, also increased before the return of the diuresis.

It was noted that the rise in specific gravity was more gradual and in some instances lagged behind the major drop in water output by as

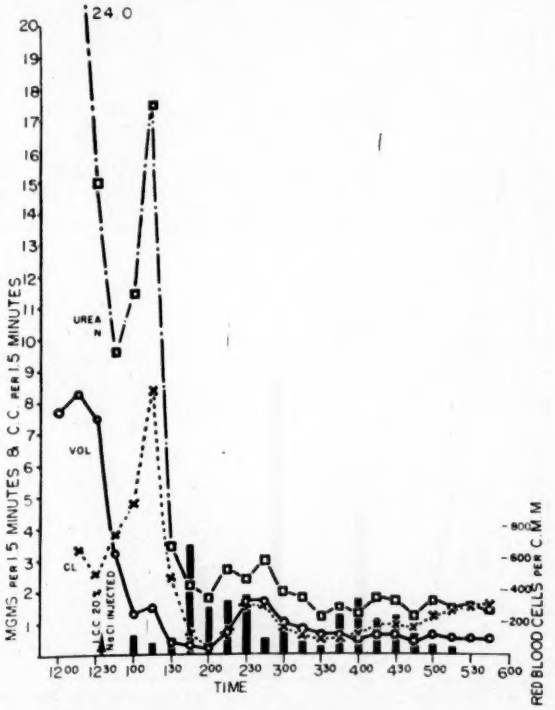

Fig. 2.—Urinary volume, chloride, urea nitrogen and red blood cell output after injection of hypertonic sodium chloride solution into the lateral cerebral ventricle of the unanesthetized dog. (Modified from Weinberg and Marx.[2])

much as two to three hours (fig. 1). In several studies this clearly reflected the change in rate of the chloride and the urea output (fig. 4). However, in other studies it probably reflected changes in rate of elimination of solid components other than those measured directly (chloride and urea).

For purposes of discussion it was convenient to consider four components of the urine: water (reported as volume of urine), chloride, urea and cellular material.

The urinary volume decreased in all studies almost immediately after the air transfer, although the extent of the decrease and the

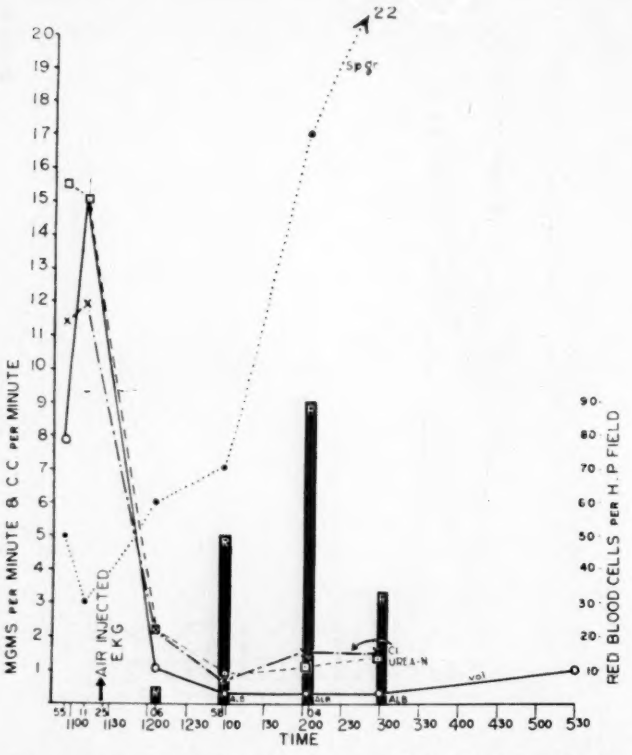

Fig. 3 (patient J. S.).—Hematuria and albuminuria following routine pneumoencephalography in man.

duration of the antidiuretic phase were variable, with the flow ranging from 15 cc. to 0.2 cc. per minute. The duration of the antidiuresis varied from one to 10 hours.

A decrease in urinary chlorides also occurred in all studies. Although the decrease roughly paralleled that of the water, there were two points of difference. In general, the drop was not so great as that shown in

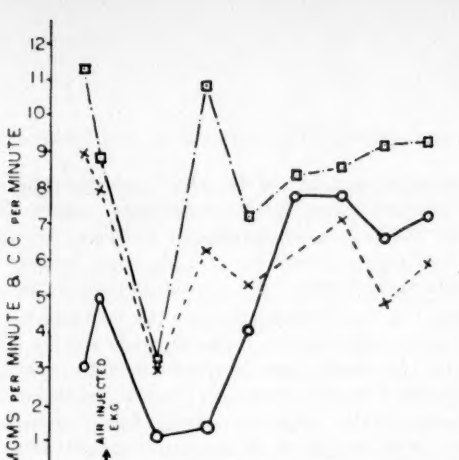

Fig. 4 (patient D. H.).—Urinary changes following ventriculography, illustrating selective renal tubular reabsorption. Circles indicate urinary volume in cubic centimeters per minute. Crosses indicate chloride level in milligrams per minute. Squares indicate urea nitrogen content in milligrams per minute.

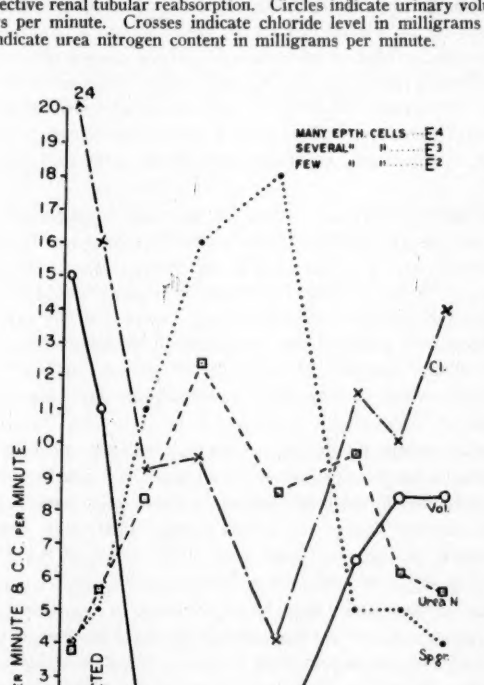

Fig. 5 (patient G.).—Urinary changes following pneumoencephalography. Selective tubular reabsorption, in particular the increase in urea nitrogen during antidiuresis, is shown.

reduction in water output, and in many cases the rate of chloride elimination increased before the increase in water output. The work of Grollman and Woods [5] on the antidiuretic principle from the pituitary has shown that during diuresis not only the water output but also the chloride output may be under control of the pituitary gland.

In general, the rate of elimination of urea decreased along with the decrease in water and chloride. However, in two of the 12 cases this did not occur. In one of these instances the rate remained constant during a protracted drop in water and chloride output and then paralleled the changes in the components during a gradual recovery period. The second case showed an actual increase in the rate of urea nitrogen output during the drop in urine volume (fig. 5). The reaction for glucose was negative in all urine specimens, and albumin appeared in only one case (fig. 3).

Similar changes are shown in figure 2, which contains reconstructed data obtained on an injection of 20 per cent solution of sodium chloride into the cerebral ventricles of the dog.[2] These data were recalculated in terms of milligrams per unit of time rather than in terms of concentration. Here again the chloride and urea decreased but not simultaneously with the water. There was a more pronounced production of the cellular components; otherwise the effects produced were nearly identical.

The variation in urinary output of the three components indicated that each was responding to its own control mechanism. However, the general trend is one of a decrease in all three, followed by a variably timed increase. Some of these differences in response could be accounted for by urine temporarily retained in the ureters and the pelves of the kidneys. However, many of the variations in urinary constituents persisted for several samples or were in apposition, such as two urea nitrogen levels which did not drop concomitantly with the decrease in the diuresis.

The table contains the changes in the cellular components of the urine. More detailed changes are shown in figures 1, 3 and 5. The round epithelial cells, red blood cells and white blood cells were reported for specimens collected during the initial diuretic phase and again during the antidiuretic period. Increases were noted in 25 of the 35 pairs of values, and in only one pair was a decrease noted.

In some studies there may have occurred in occasional instances lesions or trauma induced by the catheterization. However, it is unlikely that any such trauma would first become evident several hours after catheterization in such a high percentage of the cases, nor would the

5. Grollman, A., and Woods, B.: A New Procedure for the Determination of the Antidiuretic Principle in the Urine, Endocrinology **44**:409, 1949.

hematuria so closely and inversely follow alterations in constituent volume in both the experimental and the clinical series were trauma a factor in the appearance of the cellular elements.

Electrocardiographic records in lead II were taken for two minutes during six encephalographic and three ventriculographic procedures. The latter produced no abnormal records. During one encephalography occasional ventricular extrasystoles were seen, and during another the S-T segments were observed to become depressed. In a third encephalographic study (fig. 6) a normal record gave way to bradycardia (rate 60) after injection of the second 20 cc. of air. Coincidentally, there were skin pallor, syncope and pronounced antidiuresis. Fifteen seconds

Timed Cross Section of Urinary Cellular Components During Ventriculography and Pneumoencephalography

Patient	No. of Red Blood Cells, Control		No. of Red Blood Cells, Air Transfer		No. of White Blood Cells, Control		No. of White Blood Cells, Air Transfer		No. of Round Epithelial Cells, Control		No. of Round Epithelial Cells, Air Transfer	
	Onset of Diuresis	3 Hr. Later	Onset of Diuresis	Anti-diuretic Phase	Onset of Diuresis	3 Hr. Later	Onset of Diuresis	Anti-diuretic Phase	Onset of Diuresis	3 Hr. Later	Onset of Diuresis	Anti-diuretic Phase
Subjects with Pneumoencephalograms												
M. K.	0	0	0	40 to 50	2	2	2	80 to 90	2	5 to 10	2	40 to 50
J. S.	0	0	0	80 to 90	0	0	2	2	1	2	5 to 10	5 to 10
G.	0	0	0	0	0	0	0	2	2	2	2	40 to 50
O. C.	1	1	0	80 to 90	1	1	0	2	0	1	1	5 to 10
H. B.	0	0	0	0	2	1	1	0	2	1	2	5 to 10
D. H. (known catheterization trauma)	..	..	..	..	0	0	2	40 to 50	2	5 to 10	2	2
Subjects with Ventriculograms												
M. K.	0	0	0	0	2	2	0	1	2	5 to 10	2	2
D. H.	0	0	1	1	2	1	2	5 to 10	2	2	5 to 10	40 to 50
D.	0	1	0	1	1	2	0	5 to 10	2	5 to 10	0	80 to 90
C. E.	0	5 to 10	2	5 to 10	0	5 to 10	2	80 to 90	0	0	1	2
M.	1	0	0	0	2	2	1	40 to 50	2	1	1	40 to 50
F. B. (3½ hr.)	0	40 to 50	0	5 to 10	1	5 to 10	1	2	2	2	1	2

following completion of injection of the third 20 cc. of air, a cardiac arrest of 12 seconds' duration occurred, succeeded by nodal escape beats, a period of aberrant P waves and later nodal tachycardia, at which time the patient had regained consciousness and had a florid skin color. This patient had had no electrocardiographic abnormality during a ventriculogram taken six months previously.

Our series does not provide the broad spectrum of electrocardiographic abnormalities produced during electric shock therapy, nor do the changes approximate in variety those observed by Abeles and Schneider in their series of encephalographies.[4a] The changes do, however, provide further clinical evidence of previously observed influences,[6]

6. Korth, C.; Marx, H., and Weinberg, S. J.: Ueber die Wirkung des Strophanthins auf das Zentralnervensystem, Arch. f. exper. Path. u. Pharmakol. **185**:42, 1937.

extending even to the cardiac ventricular muscle, of purely central nervous stimuli.

Here, as in the effects on diuresis, encephalography is apparently a more potent stimulus than ventriculography. We have no explanation for this except logically to assume that the longer path taken by the air in encephalography is productive of more powerful irritation. Such an

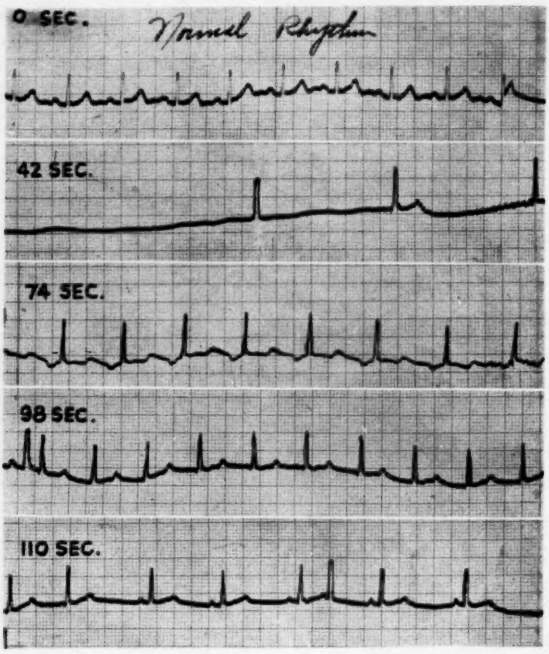

Fig. 6.—Electrocardiographic abnormalities (lead II) following pneumoencephalography.

increment could extend from the irritated spinal roots more directly to the internuncial pathways and so out the autonomic fibers to the heart.

COMMENT

The deviations from the curves for urea clearance and urinary chloride obtained on the control diuresis are obviously the result of a purely central stimulus, namely, replacement of cerebrospinal fluid by air. The effect on the kidney may result secondarily from hormonal action or from changes in blood flow. Within the central nervous

system the pathways most intimately concerned with water balance are the paraventricular and supraoptichypophysial tracts.[7] As Fisher, Ingram and Ranson [7a] have stated:

> Diabetes insipidus is essentially an hypophyseal deficiency syndrome caused by diminution or total absence of the antidiuretic hormone of the neural lobe of the hypophysis when the latter is extirpated or becomes atrophic secondary to interruption of the supra-optic-hypophyseal tracts.

An intact anterior lobe of the pituitary must be postulated,[8] acting possibly by way of diuretic adrenal cortex [9] and growth hormones.[10] The original observation on the control of urine volume by the posterior lobe of the pituitary was made by Motzfeldt,[11] who noted increased levels of posterior pituitary hormone after intravenous injection of hypertonic sodium chloride solution. Verney [7b] has elaborated on the subject, yet it is difficult to see how ependymal irritation by air in the cerebral ventricles could affect the paraventricular and supraoptic nuclear osmoreceptors postulated by Verney. More reasonable is an indirect ependymal stimulation of the intrinsic [12] antidiuretic content of the supraoptic neurons, as well as stimuli transmitted from them to the neurohypophysis.

The kidney may be affected either through endocrine, i. e., pituitary hormonal, effect on the collecting tubule or more directly by way of the nervous system. In our previous animal experiments,[2] denervation of the kidney did not prevent the renal functional changes following specific central stimuli, an observation later confirmed for afferent nerve stimuli by Theobald and Verney.[13] Camus and Roussy [14] produced

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7. (*a*) Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and Neuro-Hormonal Control of Water Balance, Ann Arbor, Mich., Edwards Bros., Inc., 1938. (*b*) Verney, E. B.: Croonian Lecture: The Antidiuretic Hormone and the Factors Which Determine Its Release, Proc. Roy. Soc., London, s. B **135**:25, 1947.

8. Richter, C. P.: Pituitary Gland in Relation to Water Exchange, A. Research Nerv. & Ment. Dis., Proc. **17**:392, 1936.

9. Silvette, H., and Britton, S. W.: Renal Function in Opossum and Mechanism of Cortico-Adrenal and Post-Pituitary Action, Am. J. Physiol. **123**:630, 1938; abstracted, Theory of Cortico-Adrenal and Post-Pituitary Influence on Kidney, Science **88**:150, 1938.

10. White, H. L.; Heinbecker, P., and Rolf, D.: Enhancing Effects of Growth Hormone on Renal Function, Am. J. Physiol. **157**:47, 1949.

11. Motzfeldt, K., cited in Walker, A. M.: Experiments upon the Relation Between the Pituitary Gland and Water Diuresis, Am. J. Physiol. **127**:519, 1939.

12. Melville, E. V., and Hare, K.: Antidiuretic Material in Supraoptic Nucleus, Endocrinology **36**:332, 1945.

13. Theobald, G. W., and Verney, E. B.: The Inhibition of Water Diuresis by Afferent Nerve Stimuli After Complete Denervation of the Kidney, J. Physiol. **83**:341, 1935.

14. Camus, J., and Roussy, G.: Le diabète insipide; son origine infundibulo tubérienne, J. méd. franç. **11**:332, 1922.

diabetes insipidus by experimental tuberal puncture even after the pituitary had been removed. The facts are not all explained by neurogenic lowering of the renal threshold alone. According to Roussy and Mosinger,[15] both the water exchange in the tissues and the excretion of water by the kidneys are affected.

The evidence of neuroregulation of thyroid dehydration with diuresis, as well as insulin water retention with oliguria, is summarized by Pick [18] and others.[16] Hepatorenal diuresis and antidiuresis, discussed by Pick [18] and by Adlersberg and Fox,[17] may or may not have central control. Posterior pituitary extract, while it has an action directly on the renal tubular epithelium, also has a hydrating action on prerenal tissue modifiable in the direction of diuresis by preliminary experimental narcosis.[18] The nervous system may also exert both a prerenal and renal [18a] vasoconstriction, at least experimentally. Whether hormones act here as intermediaries is not known. We have not determined blood or urine levels of posterior pituitary hormone in our experiments.

A determination of renal and prerenal blood flow, as well as systemic blood pressure, after ventriculography and pneumoencephalography might be productive of some interesting results. Pfeiffer and Riley,[19] employing inulin clearance tests after emotional stimuli in normal human beings, demonstrated up to 20 per cent reduction in renal blood flow, with rapid return to normal after administration of amobarbital (amytal®) sodium. Similarly, Green and Hoff [20] experimentally showed decreased renal volume and simultaneously increased limb volume on cerebral cortex stimulation, the inference being one of emergency blood transfer on the part of the organism. The hypothalamus is, of course, capable of producing either hypotension or hypertension. In prior

15. Roussy, G., and Mosinger, M.: Le tuber cinereum et son rôle dans les principales fonctions du métabolisme: métabolisme de l'eau, des glucides et des lipids, Ann. de méd. **33**:193, 1933.

16. Gaunt, R.; Birnie, J. H., and Eversole, W. J.: Adrenal Cortex and Water Metabolism, Physiol. Rev. **29**:291, 1949.

17. Adlersberg, D., and Fox, C. L., Jr.: Changes of the Water Tolerance Test in Hepatic Disease, Ann. Int. Med. **19**:643, 1943.

18. Glass, A.: Ueber den Wasserwechsel des Säugetiermuskels unter verschiedenen experimentellen Eingriffen, Arch. f. exper. Path. u. Pharmakol. **136**:72, 1928. Kugel, M. A.: Hypnotika und Diurese: Studien über die Wasser- und Kochsalzausscheidung im Schlaf mit und ohne Hypophysenwirkung, ibid. **142**:166, 1929.

18a. Trueta Raspall, J., and others: Studies of the Renal Circulation, Oxford, England, Basil Blackwell & Mott, Ltd., 1947.

19. Pfeiffer, B., and Ripley, H. S.: Measurement of Renal Blood Flow and Glomerular Filtration During Variations in Blood Pressure Related to Changes in Emotional States and Life Situation, J. Clin. Investigation **26**:1193, 1947.

20. Green, H. D., and Hoff, E. C.: Effect of Faradic Stimulation of the Cerebral Cortex on Limb and Renal Volumes in Cat and Monkey, Am. J. Physiol. **118**:641, 1937.

animal experiments [21] intraventricular administration of hypertonic sodium chloride solution, such as was shown to produce hematuria, also resulted in a notable and protracted elevation of blood pressure. It is, therefore, unlikely that the alterations in renal function in our clinical studies depend on a lowered systemic blood pressure. The observed changes in renal function as a result of a stimulus originating within the central nervous system are not absolutely dependent on production of either hypertension or hypotension. However, it is possible that circulatory changes in other organs of the body may secondarily affect rate of blood flow in the kidney and so contribute to the antidiuresis and other observations in our studies.

Recently, we have come to recognize the diuretic actions of the adrenal cortex hormones,[16] with the probability of balanced activity between these hormones and that of the posterior part of the pituitary gland. Thus, antidiuretic substances of the pituitary are either more abundant or more potent in adrenalectomized animals. The hyper-adrenocortical state is characterized by diuresis, and, inasmuch as the adrenal gland is under close nervous control, it is not likely that the undoubted action of the corticosteroids on renal tubular epithelium plays a major part in the antidiuresis following ventriculography and encephalography.

Whatever, in addition to a stimulated secretion of hormones of the posterior lobe of the pituitary, may be the mechanism of the action on the kidneys, it is probable that the antidiuretic response is an analog of similar response seen in the initial phase of the "adaptational syndrome." [22] If so, it is probable that administration of pituitary adrenocorticotropic hormone (ACTH) or cortisone will prevent or minimize the anuria following ventriculography or encephalography, as seen in figure 1 detailed above, and modify the pattern observed in our series.

The antidiuretic response has for the past half century been observed as a result of afferent surgical stimuli, and Moyer [23] in his review of the work of Coller and his associates presented a summary of renal functional alterations following major surgical procedures, not including neurosurgical measures. Similar antidiuresis was observed after pain stimuli by Wolf.[24]

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21. Weinberg, S. J.: Experimentelle Untersuchungen über die zentrale Regulation der Vasomotoren, Arch. f. exper. Path. u. Pharmakol. **178**:397, 1935.

22. Browne, J. S. L.; Karady, S., and Selye, H.: Effect of Noxious Agents on Creatine, Creatinine, Chloride and Water Excretion, J. Physiol. **97**:1, 1939. Selye, H.: The Adaptation Syndrome, J. Clin. Endocrinol. **6**:143, 1946.

23. Moyer, C. A.: Acute Temporary Changes in Renal Function Associated with Major Surgical Procedures, Surgery **27**:198, 1950.

24. Wolf, G. A.: The Effect of Pain on Renal Function, A. Research Nerv. & Ment. Dis., Proc. **23**:358, 1943.

The anuria of major surgical intervention is categorically stated by Moyer not to be due to the anesthetic agent. It is presumed to follow afferent nervous stimulation. Our search of the literature has brought to light no previous observation of the effect on the kidney in man following the introduction of air into the ventricular system. Anuria following ventriculography and pneumoencephalography has received little attention. Pertinent to the subject is the emphasis given by Schmidt [25] to the frequency of occurrence of oliguria with intracranial tumors.

The duplication in man of renal functional alterations following central nervous system stimuli, as previously demonstrated in the dog, would merely signify transient or acute change within physiological limits, were it not for the fact that in some of the animal studies [2] the changes went beyond the physiological to the extent of pronounced albuminuria and gross hematuria in experiments involving both continuous forced diuresis and fluid restriction. The albumin and blood appeared in concentrated urine at the height of the antidiuresis. In our clinical studies hematuria occurred during both encephalographic and ventriculographic procedures, and blood also appeared in concentrated urine during antidiuresis. In these cases no observations were made under conditions of fluid restriction.

The hematuria, albuminuria and antidiuresis were severer in the subjects with encephalograms as contrasted to those with ventriculograms. The latter procedure, performed after passing a needle into the lateral ventricle, is relatively painless. Such headache as occurs is probably due to change in intracranial tension and direct irritation from the injected air. Pneumoencephalography, on the other hand, requires replacement of both spinal and ventricular fluids by 60 to 80 cc. of air injected into the lumbar subarachnoid space and is accompanied with considerable headache, hyperhidrosis and variable degrees of bradycardia and hypotension. Here nerve roots, as well as the ependyma, are irritated, and the central stimulation is more powerful. We have made no other attempt to evaluate the relative importance of any psychic trauma from pain, as contrasted with the irritative action on the ependyma of injected air, in causation of the urinary functional changes. In the experiments with unanesthetized animals previously cited,[2] alkaloidal and hormonal agents causing no perceptible pain produced antidiuresis, hematuria and albuminuria. Similarly, pain was minimal in patients subjected to ventriculography and in several undergoing encephalography.

Marx [26] was able to produce hemoglobinuria and pathological changes of chronic glomerular nephritis in rats following large doses

25. Schmidt, R.: Ueber Hirntumor-Oligurie, Klin. Wchnschr. **12**:105, 1933.
26. Marx, H.: Unpublished data, 1934.

of posterior pituitary extract. Later, renal structural changes in rats, in the nature of a tubular degeneration, were produced by Byron [27] using vasopressin injection (pitressin®). Brobeck and his associates [28] produced in rats, following experimental hypothalamic lesions, chronic glomerulonephritis with albuminuria and hematuria. This observation was confirmed by Kennedy, in London.[29] In 1931 one of us demonstrated experimentally rupture of intestinal capillaries after administration of vasopressin.[30] Whether the hematuria is analogous or not is only conjectural. The data on hand are not yet sufficient to postulate that the pathological changes in nephritis might follow repeated insults of the "adaptational" type. The mechanism is shown to exist for this, and experimental evidence is now extended to include the human organism.

SUMMARY AND CONCLUSIONS

In 10 male patients undergoing controlled diuresis, ventriculography and pneumoencephalography was accompanied with antidiuresis, reduction in output of urinary chloride and nitrogen and, in several instances, electrocardiographic changes. In the majority of these studies red blood cells appeared in the urine during antidiuresis, together with white blood cells, round epithelial cells and, in one case, albumin.

The evidence supports the hypothesis that the urinary fluctuations in chloride, urea and volume are independent, each constituent having its own control mechanism.

The evidence favoring a central regulating mechanism responsible for anuria and nephritis is discussed.

Miss Jane Yarborough, Miss Norma Claunch, R. N., Mr. Saul Kanter and Mr. E. B. Farrar gave laboratory and other technical assistance.

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28. Brobeck, J. R.; Tepperman, J., and Long, C. N. H.: Experimental Hypothalamic Hyperphagia in the Albino Rat, Yale J. Biol. & Med. **15**:831, 1943.

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30. Weinberg, S. J.: Intestinal Bleeding Following Administration of Posterior Pituitary Extracts, J. Pharmacol. & Exper. Therap. **41**:165, 1931.

STUDIES OF IMMUNOLOGIC REACTIONS OF PATIENTS WITH HODGKIN'S DISEASE

Antibody Reaction to Typhoid Immunization

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ALTHOUGH the exact mode and site of antibody production are subject to debate, it appears evident that the lymphoreticuloendothelial system participates in this process.[1] Hence, one might expect that a generalized disease affecting that system might also alter normal immunologic responses. That the latter may occur is suggested by the high incidence of tuberculin energy [2] and the general "poverty of the

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immunological response" in patients with Hodgkin's disease, resulting in "their increased susceptibility to infection."[3]

In five years of close clinical contact with more than 150 patients who had Hodgkin's disease, no greatly increased incidence of intercurrent disorders, such as infections of the upper respiratory tract, pneumonitis, pharyngitis, sinusitis, furunculosis and infections of biopsy wounds, was noted. Since this experience was at variance with the opinion expressed in the above quotation, we were prompted to make a more objective investigation of the immunologic responses of our patients.

MATERIALS AND METHODS

As an indicator, we used typhoid-paratyphoid vaccine and measured the response with frequent agglutination tests.

The mouse protection test offers a better measure of the potency of the immunizing substance, since there is no fixed relationship between the amount of agglutination present and the degree of protection following vaccination. Our main interest lay, however, in the amount of antibody protein the diseased lymphoreticuloendothelial system of these patients could manufacture under an adequate stimulus. Consequently, we measured the response to immunization by agglutination tests rather than by the mouse protection test.

Thirteen patients with Hodgkin's disease (proved by biopsy in all cases) were given a standard immunizing course with a bacterial vaccine containing 1,000,000,000 Bacillus typhosus (Salmonella typhosa) and 750,000,000 Bacillus paratyphosus A and B (Salmonella paratyphi and Salmonella schotmuelleri) organisms per milliliter.[4] The vaccine was administered intramuscularly in three doses, 0.5, 1.0 and 1.0 ml., at weekly intervals.

Eight other patients with Hodgkin's disease received, in addition to the vaccine, a therapeutic course of nitrogen mustard (methyl-*bis*[beta-chloroethyl]amine hydrochloride and *tris*[beta-chloroethyl]amine hydrochloride) in total dose of 0.5 mg. per kilogram of body weight.

Twenty-nine student nurses were used as controls for the potency of the vaccine.

Agglutination tests were carried out by the slow macroscopic technic with H and O antigens.[4] Tests were done at two-week intervals for the first six weeks and monthly thereafter in most cases for four to five months. A total of 120 agglutination tests was carried out on the group of 21 patients.

RESULTS

Table 1 shows the results of immunization in all patients and controls in terms of the highest titer reached during a period four to 12 weeks after the first injection of vaccine.

Eighty-six per cent of the patients and 80 per cent of the controls attained H titers of 1 : 320 or more, while 80 per cent of the patients and 83 per cent of the controls attained O titers of 1 : 80 or more. The

3. Dubin, I. N.: The Poverty of the Immunological Mechanism in Patients with Hodgkin's Disease, Ann. Int. Med. **27**:898-913, 1947.

4. The vaccine and antigens were supplied by the Division of Laboratories and Research, New York State Department of Health.

mean H titer for the patients was 1:2,090 and for the controls 1:1,280, while mean O titers for patients and controls were 1:610 and 1:740, respectively.

Table 2 shows the agglutinin titers of eight patients who were given therapeutic courses of nitrogen mustard at varying times during immunization.

TABLE 1.—*Agglutinin Titers of Patients with Hodgkin's Disease and Controls*

Number of Patients		Highest Titer Reached During Period 4 to 12 Wk. After Immunization	Number of Controls	
H Antigen	O Antigen		H Antigen	O Antigen
2	0	1:10,240	1	1
2	0	1:5,120	0	1
1	2	1:2,560	5	0
5	3	1:1,280	6	0
5	3	1:640	4	2
3	4	1:320	7	8
0	4	1:160	2	6
1	1	1:80	1	6
0	0	1:40	1	2
0	1	1:20	0	1
2	3	No agglutination	2	2

TABLE 2.—*Effect of Administration of Nitrogen Mustard on Typhoid Immunization*

Patient No.	Titer	Weeks After First Dose of Vaccine								Time of Nitrogen Mustard Administration
		0	1	3	5	7	9	12	16	
1	H	0	0	1:40	1:80	1:320	1:160	1:80	0	2 wk. prior to 1st dose of vaccine
	O	0	0	1:20	1:40	1:80	1:20	1:20	0	
2	H	0	1:2,560	1:10,240	....	1:10,240	.....	....	1:10,240	With 1st dose of vaccine
	O	0	1:2,560	1:1,280	....	1:1,280	.....	....	1:320	
3	H	0	0	0	....	0	.....	0	.....	With 1st dose of vaccine
	O	0	0	0	....	0	.....	0	.....	
4	H	0	0	1:5,120	1:1,280	.....	.....	....	.....	With 2d dose of vaccine
	O	0	0	0	0	.....	.....	....	.....	
5	H	0	.....	0	....	0	0	....	.....	With 2d dose of vaccine
	O	0	.....	0	....	0	0	....	.....	
6	H	0	1:640	1:1,280	1:1,280	.....	1:2,560	....	.....	With 3d dose of vaccine
	O	0	1:160	1:160	1:160	.....	1:1,280	....	.....	
7	H	1:640	.....	1:640	1:1,280	.....	1:160	....	1:40	2 wk. after 3d dose of vaccine
	O	1:160	.....	1:80	1:640	.....	1:40	....	1:20	
8	H	1:160	1:640	1:640	1:640	.....	1:160	....	1:40	3 wk. after booster dose
	O	0	1:320	1:640	1:160	.....	1:40	....	1:20	

Patient 1 was given a course of nitrogen mustard, and when the effect was most pronounced, as evidenced by leukopenia, administration of vaccine was begun. His response was somewhat delayed, and agglutinins had disappeared four months after immunization. Responses of this type (rapid loss of agglutinins) were also seen in four other patients who did not receive any nitrogen mustard.

Patients 2 and 3 were given nitrogen mustard simultaneously with the first dose of vaccine. While one did not develop any agglutinins at all, the other showed high titers.

Patients 4 and 5 were given nitrogen mustard with the second dose of vaccine. One showed a sharp initial rise in H titer but was temporarily lost for follow-up studies. The other did not develop any agglutinins. Four months later patient 5 still had no agglutinins and was given a second course of immunization. Her H and O titers were 1:640 and 1:80, respectively, five weeks later.

In patient 6 the agglutinin titer rose after administration of nitrogen mustard, while in patients 7 and 8 it dropped.

COMMENT

Patients with Hodgkin's disease are quite capable of producing normal amounts of antityphoid agglutinins after an adequate stimulus. This appears to be true regardless of the duration or stage of the disease. Although no special effort was made to select patients on the basis of the severity of the disease process and its duration, subsequent events have shown that the group studied can be divided into categories according to prognosis. Eighteen months after the immunizations were carried out, nine of the patients were dead and 12 still living.

Analysis of the response to immunization of these two groups simply on the basis of the highest agglutinin titer attained shows no correlation with prognosis. However, analysis of the pattern of agglutinin response over a period of time shows that five patients demonstrated an inability to maintain normal titers for more than two to three months (see table 2, patient 1). The condition of all five of these patients was classified as advanced on a clinical basis. Four died within eight months, and the fifth died within 15 months, of immunization.

Spurr [5] has shown that nitrogen mustard interferes with agglutinin production in normal rabbits when the drug is administered simultaneously with the vaccine. The agglutinin response in our patients treated with nitrogen mustard was so variable and the number of patients tested so small that it is impossible to demonstrate any effect of nitrogen mustard on immunologic mechanisms in human subjects. In some patients nitrogen mustard apparently does not interfere with agglutinin production (table 2, patient 2); in others the drug appears to inhibit agglutinin production entirely (patients 3 and 5). Administration of nitrogen mustard may be followed by a rise in agglutinin titer (patients 2, 4 and 6) or a fall (patients 7 and 8).

The question of the degree of susceptibility of patients with Hodgkin's disease to intercurrent infection must necessarily remain a matter of personal opinion, since it defies any critical analysis. Close observation of a large number of patients over a period of five years in a locality

5. Spurr, C. L.: Influence of Nitrogen Mustards on Antibody Response, Proc. Soc. Exper. Biol. & Med. **64**:259-261, 1947.

where crowding and climate tend to produce a high incidence of infections of the respiratory tract has not confirmed the theory that these patients are more susceptible.

SUMMARY

Patients with Hodgkin's disease can respond to typhoid immunization with rise of agglutinin titers to normal levels. Some patients with advanced disease show inability to maintain agglutinins for more than three months. In a small series of patients the effect of nitrogen mustard on production of antityphoid agglutinin is inconstant.

GANGRENE OF THE EXTREMITIES

A Recently Recognized Complication of Severe Meningococcic Infection

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WITH RARE exception,[1] the extensive literature on meningococcic infection is singularly free—until recent years—of references to a serious complication, gangrene of the extremities. By contrast, a growing but still limited number of case reports has appeared since 1944.[2] An analysis of this material and a description of another case comprise the following report.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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2. (*a*) Bernstein, P.: Causalgia and Gangrene: Rare Complications in Meningococcal Meningitis; Report of a Case, New England J. Med. **230**:482-483 (April 20) 1944. (*b*) Hayes, J. M., and Whalen, J. F.: Fulminating Meningococcemia (Waterhouse-Friderichsen Syndrome): An Unusual Case with Recovery Following Treatment with Penicillin, J. A. M. A. **127**:645-646 (March 17) 1945. (*c*) Smith, L. B.; Alpern, E. B.; Shapiro, J., and Kissane, M. M.: Meningococcemia with Gangrene: Report of the Recovery of a Case in Which Meningococci Were Found in Direct Blood Smears, Arizona Med. **3**:25-30 (Jan.) 1946. (*d*) Malagueta, I., and Renault, G.: Moléstia de Weichselbaum e gangrena das extremidades, Rev. méd. munic. **10**:94-114 (April-June) 1947. (*e*) Hill, W. R., and Kinney, T. D.: The Cutaneous Lesions in Acute Meningococcemia: A Clinical and Pathologic Study, J. A. M. A. **134**:513-518 (June 7) 1947. (*f*) Grubschmidt, H. A.; Graham, G. C., and Jessup, E. C.: A Case of Fulminating Meningococcemia Exhibiting the Waterhouse-Friderichsen Syndrome and Demonstrating the Values of Cortical Extract Administration, Ann. Int. Med. **26**:294-304 (Feb.) 1947. (*g*) Broders, A. C., Jr., and Snell, A. M.: Fulminating Meningococcemia with Gangrene, Am. J. Med. **3**:657-660 (Nov.) 1947. (*h*) DeFuccio, C. P., and Dresner, E. E.: Meningococcemia with Meningitis Accompanied by Bilateral Gangrene of the Lower Extremities (Waterhouse-Friderichsen Syndrome), Pediatrics **3**:837-838 (June) 1949.

REPORT OF A CASE

On Sunday night, Nov. 6, 1949, a 28 year old Negro man was brought to the emergency room of Halloran Veterans Administration Hospital in semicoma. The history, as obtained from his mother and stepfather, indicated that the patient was honorably discharged from the United States Army in February 1944, with a diagnosis of acute rheumatic fever, and from then on he was presumed to have "heart trouble." Since his discharge from the Army, he was subject to periodic attacks, characterized by pains, aches, weakness and "fever," persisting for a week and followed by full recovery. During these attacks mentally unclear periods of several hours occurred and, reputedly, fecal incontinence. None of the attacks was treated medically. In midafternoon, November 5, generalized aches, weakness and a frontal headache developed. These manifestations were soon followed by fever, shaking chills, vomiting, diarrhea and mental confusion. This was considered to be another of his "attacks," although exaggerated, and a local physician was not called until 24 hours later, at which time a single injection of penicillin was given and hospitalization recommended.

It was obvious on admission that the patient was critically ill. He thrashed about restlessly and did not respond to ordinary stimuli. The temperature was 99.8 F.; the pulse was barely perceptible, with a rate of 120 per minute, and the respirations were shallow at a rate of 50 per minute. Dehydration was moderate. A small amount of blood was noted in the mouth. Also noted were dental caries, moderate pharyngeal injection and faint heart sounds. No murmurs were heard. The blood pressure was 50/40 mm. Hg. The results of physical examination were otherwise remarkably normal. The lungs were clear; the skin was dark brown but showed no obvious petechiae; the neck was supple, and there were no abnormal neurological reflexes.

The problem of differential diagnosis, which included acute bacterial endocarditis, addisonian crisis and other diseases, was resolved quickly by a spinal puncture which showed an initial pressure of 220 mm. of water and cloudy fluid. The white blood cell count was 8,650 per cubic millimeter; the cells were predominantly polymorphonuclear leukocytes. A direct smear showed many gram-negative intracellular diplococci. Total protein was 468 mg. per 100 cc. The blood studies disclosed 14 Gm. of hemoglobin and 4,500,000 red blood cells and 20,500 white blood cells per cubic millimeter, with 89 per cent polymorphonuclear cells, 10 per cent lymphocytes and 1 per cent monocytes.

Shortly after reaching the ward, the patient showed some signs of improvement; the blood pressure increased to 90/50, and, although still confused, he began to complain of pains in his neck, back and legs. The pulse remained rapid; the skin had become cold and clammy.

He received 5 Gm. of sodium sulfadiazine intravenously and 200,000 units of aqueous penicillin intramuscularly at once. Large amounts of fluids were administered intravenously (isotonic sodium chloride solution, 5 per cent dextrose solution, lactated Ringer's solution), and a 500 cc. blood transfusion was given within the first day. Penicillin therapy was continued in doses of 200,000 units given intramuscularly every three hours for four days and then changed to doses of 100,000 units. From November 15 on, one or two daily injections of 300,000 units of procaine penicillin were administered. Sulfadiazine, in 1.5 Gm. doses for two days and 1 Gm. doses thereafter, was given orally, together with 3 Gm. of sodium bicarbonate every four hours for the following 11 days.

Consciousness returned gradually to normal during the first few days, and, as it did, nuchal rigidity became evident. The temperature climbed to 102.8 F. on the second hospital day and returned to 100 F. by lysis at the end of a week.

Thereafter low grade fever (100 F.) persisted. The pulse rate hovered at 120 per minute for two days and thereafter descended to 70 to 90 per minute. The blood pressure remained, with minor fluctuations, at 90-80/60-50 mm. Hg for four days and then rose rapidly to average levels of 120/70, where it remained.

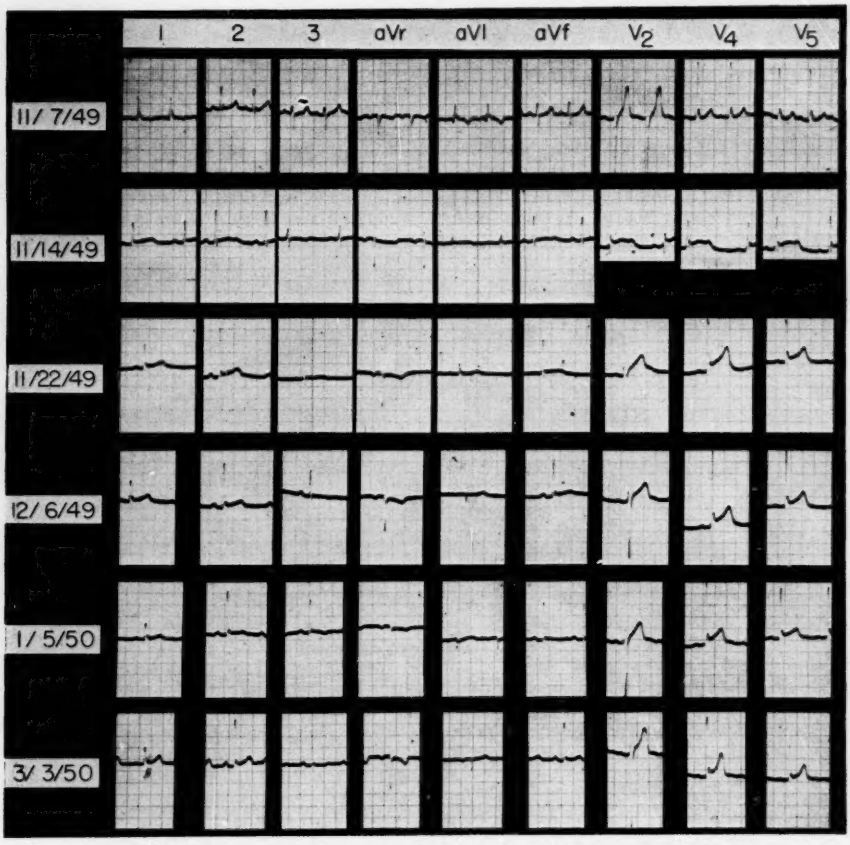

Fig. 1.—Electrocardiogram of Nov. 7, 1949 shows sinus tachycardia and left axis deviation. R/S ratio in chest leads and T wave inversion in leads I and aVL suggest left ventricular enlargement and myocardial damage. Electrocardiogram of Nov. 14, 1949 shows regular sinus rhythm. S-T elevation in leads I, II, aVL, aVF and V_3, V_4 and V_5 indicates acute pericardial involvement; greatly prolonged Q-T interval indicates myocardial involvement. Subsequent tracings show a gradual return to normal of the Q-T intervals, S-T level and T waves. Electrocardiogram of March 3, 1950 shows S-T elevation of questionable significance and possibly normal for this patient.

But the patient's course was extremely uneven. During the first few days, his condition continued to improve impressively, even though a variety of complications ensued.

1. For several days there were three to four watery nonbloody diarrheal stools daily.

2. The tachypnea (40 to 50 per minute) noted on admission persisted, and on the morning of November 8 he was found to have extensive bronchopneumonia bilaterally on both physical examination and roentgenogram. Use of an oxygen tent gave considerable relief. By November 11, respiratory symptoms were absent and signs were minimal.

3. On the second hospital day an acute, extensive herpetic eruption appeared on the lips and on the entire lower two thirds of the left side of the face. This was confirmed to be herpes simplex by the dermatologist. Treatment was local.

4. The cardiac status was followed closely from the beginning, in view of the past history and the possibility of endocarditis, and also in view of the severe

Fig. 2.—Gangrene on right hand.

infection. The heart, on repeated examinations by fluoroscopy and roentgenography, showed no apparent abnormality. A short apical systolic murmur was heard, but there was no evidence of rheumatic endocarditis. The only abnormalities present were electrocardiographic. Serial electrocardiograms showed progressive changes (fig. 1).

5. By November 10 small, sharply defined gangrenous areas were observed on the skin of the right forearm, right middle finger, left hand and thumb, left knee and lower part of the back. In the course of several weeks, the lesions became crusted, then clearly ulcerated and ended in healed, depressed scars. The most extensive lesion (fig. 2) became converted into a large blister which shriveled slowly, eventually also ending in a depressed scar.

6. As the patient recovered consciousness, he complained of some generalized aches and pains, but most of all of pain and tenderness in his feet. On November 10 an irregular, but sharply demarcated, dark bluish, swollen area was noted over the dorsum of his left foot (fig. 3). The major portions of all five toes were even darker in color. The toes themselves were cool, but the entire dorsal area

was warm. The pulsations in the posterior tibial, peroneal and dorsalis pedis arteries were palpated bilaterally at this time. The balls of both feet were exquisitely tender to touch, even though no visible abnormality was present on the right. The patient was also studied at this time in the peripheral vascular clinic with a battery of tests. The only significant observation was the obvious impending gangrene of the toes of the left foot. No abnormality was noted in the larger arteries. Several observers confirmed the presence of good pulsations in the arteries, including the left dorsalis pedis. On the same day (November 10) a left lumbar sympathetic block was induced with injection of 1 cc. of 10 per cent piperocaine (metycaine®) hydrochloride solution at the first, second and third lumbar vertebrae, with equivocal results. This was repeated on the following day with definitely negative results. There was no change in skin temperature or clinical appearance. In succeeding days the toes became progressively darker, almost black, and drier. The dorsum of the left foot remained warm, although it, too, became darker. On November 18 the pulsation in the left dorsalis pedis artery

Fig. 3.—Gangrene of left foot. Left, dorsal view; right, plantar view.

could no longer be felt, but the other arterial pulsations remained strong. The tenderness in the soles of both feet diminished very slightly. Prophylactic administration of penicillin was continued, preparatory to amputation, which was performed on December 9 in the midleg region, with the patient under anesthesia induced with cyclopropane. Convalescence was uneventful.

Of interest was the fact that the right foot later showed extensive deep desquamation of the sole and heel. The tenderness in the ball of this foot also persisted and faded slowly. At the end of January there was still some residual tenderness, although the patient could stand on the foot. Repeat testing on Feb. 2, 1950 did not demonstrate any abnormal behavior of the vessels. Comparison of roentgenograms of the right foot taken on Dec. 5, 1949 and on Jan. 17, 1950 disclosed extensive osteoporosis in the latter film.

The significant laboratory data were as follows: The total leukocyte count rose to 30,000 per cubic millimeter on the third hospital day and gradually returned to a normal range two weeks later. The early urine specimens showed consistent albumin (1 + to 3 +), some red blood cells and a few granular casts. The urine became completely normal within a few weeks. The serologic tests

for syphilis gave a negative reaction. No cold hemolysins or agglutinins were detected in the serum. Brucella agglutinins were present only as 2 + readings in dilutions up to 1: 80. The antistreptolysin 0 titer was 400 to 500 units per cubic centimeter in a single specimen. The initial blood culture was positive for Meningococcus group II alpha, but all subsequent cultures failed to yield the organism on mediums containing both paraaminobenzoic acid and penicillinase. The initial specimen of spinal fluid was negative on culture, though organisms were seen on direct smear. The spinal fluid specimen taken Nov. 17, 1949 was normal in all respects.

An addendum to the history was obtained when the patient was well. In childhood he had had diphtheria and chickenpox. Two months after being drafted into the United States Army, in late 1943, he had fever (102 F.), swelling of the fingers and left knee and pain in the back. He received a certificate of disability discharge from the Army two months later, although he was told that everything was "normal." Since then, he had had recurrences of joint swelling and fever at frequent intervals. Each attack subsided within a week. He denied frequent sore throat or any cardiovascular symptoms. There was no cleancut history of epilepsy.

The present illness, as told by the patient, began abruptly. He had had a loose cough for two months but otherwise felt very well. On the day prior to his admission to the hospital, he was doing some household chores, when suddenly about noon he became very weak—"couldn't move a muscle." Shortly thereafter, he noticed a sore throat and excruciating diffuse pain developed in both feet. There was no headache. The pain in his feet became "unbearable," and his memory remained blank until 48 hours later in the hospital.

Prior to his discharge from the hospital, except for the electrocardiographic residua of the recent pericarditis and myocarditis, no evidence of old rheumatic heart disease was seen. Neurological examination also gave normal results. The electroencephalogram showed a few equivocal changes, not believed to be characteristic of epilepsy.

The patient was discharged from the hospital on March 3, 1950.

Pathological Observations (Dr. G. E. Muehsam).—The gross appearance of the amputated left leg was as described above (fig. 3). Dissection of the major arteries of the foot and their branches included the anterior tibial, posterior tibial, peroneal and arcuate arteries. All arteries, on multiple section, were soft, pliant and had patent lumens. The only exception was the anterior tibial (and dorsalis pedis) artery, in which, beginning about 2.5 cm. below the malleoli and extending for 6 cm., the lumen was occluded by a moderately soft and friable but adherent thrombus.

Microscopic sections of many areas did not show acute inflammatory reaction, but considerable necrosis superficially and chronic granulation tissue in the corium were seen. Many of the small arterioles had thickened walls and were surrounded by loose perivascular collections of lymphocytes. Cross section of the anterior tibial and dorsalis pedis arteries showed a relatively fresh thrombus in the center, with early organization at the periphery where it was firmly attached to the vessel wall. The veins were not remarkable, except when situated in an actual necrotic area. The peripheral nerve branches showed extensive demyelination.

COMMENT

Even a limited survey of the voluminous literature on meningococcic infection demonstrates clearly how rare complicating gangrene of the extremities is. In his several textbook accounts of meningococcic

meningitis in the years between World Wars I and II, Herrick [3] mentioned this complication briefly. However, Dopter's comprehensive book [4] in 1921 discussed "malignant purpuric fever" and only gangrene of the skin. Brinton's clinical monograph [5] in 1940 had only a casual reference to gangrene of the skin. In more recent accounts, Thomas,[6] in a study of 1,518 cases, Steiner,[7] in a review of 2,623 cases from the literature between 1943 and 1945, Kinsman,[8] Hoyne and Brown,[9] Daniels [10] and Banks,[11] in a report of 706 consecutive cases between 1939 and 1947 in England, failed to mention gangrene of the extremities, although gangrene of the skin is described as a rare complication.

An exhaustive search of the literature was not made. However, since 1944 publication of nine isolated reports of gangrene of the extremities has been noted. Prior to this date only two case reports have been found. No definitive explanations are at hand for the recent appearance or for the mechanism of this gangrene. Analysis of the reported cases (table) permits a few generalizations but also raises new problems.

Age and Sex.—Of the 10 reported cases in which age and sex were given, the sex distribution was about equal (6 males, 4 females), but only two of the 10 cases were of children (7 and 14 years of age); the remainder were of young adults. Yet Banks [11] stated that the highest mortality in meningococcic infection occurs in the very young and the aged. Levinson [12] considered meningococcic meningitis to be primarily

3. Herrick, W. W.: Cerebrospinal Fever, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, pp. 213-221.

4. Dopter, C.: L'infection méningococcique, Paris, J. B. Baillière et Fils, 1921.

5. Brinton, D.: Cerebrospinal Fever, ed. 6, Baltimore, Williams & Wilkins Company, 1941.

6. Thomas, H. M., Jr.: Meningococcic Meningitis and Septicemia: Report of Outbreak in Fourth Service Command During Winter and Spring of 1942-1943, J. A. M. A. **123**:264-272 (Oct. 2) 1943.

7. Steiner, M.: Cerebrospinal Fever Complicated by Extensive Thrombotic Gangrene of Skin and Subcutaneous Tissues, with Recovery, U. S. Nav. M. Bull. **47**:523-528 (May-June) 1947.

8. Kinsman, J. M.; D'Alonzo, C. A., and Russi, S.: Fulminating Meningococcic Septicemia Associated with Adrenal Lesions: An Analysis and Discussion of 7 Cases, Arch. Int. Med. **78**:139-169 (Aug.) 1946.

9. Hoyne, A. L., and Brown, R. H.: 727 Meningococcic Cases: An Analysis, Ann. Int. Med. **28**:248-259 (Feb.) 1948.

10. Daniels, W. B.: Meningococcic Bacteremia, Arch. Int. Med. **81**:145-161 (Feb.) 1948.

11. Banks, H. S.: Meningococcosis: A Protean Disease (Milroy Lecture), Lancet **2**:635-640 (Oct. 23); 677-681 (Oct. 30) 1948.

12. Levinson, A.: Meningitis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 4, chap. 8, p. 44.

a disease of children and stated that 80 per cent of endemic cases occur before the age of 10 and 50 per cent before the age of 5, the largest number of cases occurring in the first two years of life. During epidemics, age is of less importance.

Summary of Data from the Literature on Twelve Patients with Gangrene of the

Case No.	Authors	Age	Sex	Culture		Meningitis	Meningococcus Type	Severity of Illness	Extent of Skin Gangrene
				Blood	Spinal Fluid				
1	Elliott and Kaye,[1a] 1917	23	M	—	+	+	N. d.*	Patient delirious during first few days	++
2	Herrick,[1b] 1918	N. d.	N. d.	N. d.	N. d.	+	N. d.	Probably severe	N. d.
3	Bernstein,[2a] 1944	34	F	N. d.	N. d.; gram-negative diplococci on direct smear	+	N. d.	Very severe	+++
4	Hayes and Whalen,[2b] 1945	27	F	N. d.	N. d.	N. d.	N. d.	"Waterhouse-Friderichsen syndrome"	++
5	Smith and others,[2c] 1946	20	M	+ Meningococci found in direct blood smear	N. d.	+	N. d.	Fulminating	+++; 40% of body involved
6	Malagueta and Renault,[2d] 1947	14	M	—	—	+	N. d.	Coma on admission	++
7	Malagueta and Renault,[2d] 1947	38	F	N. d.	+	+	N. d.	Severe	++
8	Hill and Kinney,[2e] 1947	N. d.	N. d.	+	N. d.	N. d.	N. d.	N. d.	N. d.
9	Grubschmidt and others,[2f] 1947	17	F	+	—	—	N. d.	"Waterhouse-Friderichsen syndrome"	++
10	Broders and Snell,[2g] 1947	18	M	+	—	—	IIa	Fulminating	++
11	DeFuccio and Dresner,[2h] 1949	7	M	+	+	+	II	"Waterhouse-Friderichsen syndrome"	N. d.
12	Weiner, 1950	28	M	+	— Gram-negative diplococci on direct smear	+	IIa	Fulminating	+

* N. d. signifies no data available.

Meningococcemia, Meningitis and Meningococcus Type.—No apparent relationship with the meningitis per se is discernible. Two of the recently described patients had no meningitis. The meningococcemia, however, is probably a paramount factor. Is the Meningococcus type of importance? It has long been known that there are immunologic and epidemiological differences between types I and II. For instance, the

epidemic cases usually show type I organisms and sporadic cases type II.[13] Such data were available only in the last three cases (table). Type II meningococci were reported in one case and type II alpha meningococci in two.

Extremities Associated with Meningococcic Infection

Gangrene of the Extremities			
Signs and Symptoms First Noted	Extent of Involvement	Treatment	Comment
Feet cold at onset of illness; early signs noted on 3d day	Both feet, above malleoli; finger tips "shriveled and blue"	N. d.	Associated frostbite; bilateral amputation of both feet above malleoli
N. d.	"Gangrene of toes"	Massive intravenous and intraspinal administration of antimeningococcus serum	.....
Generalized pain including extremities at onset; excruciating pain in feet early in disease; dry gangrene on 8th day	3 toes on right foot; 2 toes on left foot	Immediate with sulfadiazine	Persistent causalgia-like pain of right arm and hand; amputation of affected toes; late osteoporosis
Pain in extremities and feet from onset; early gangrene of toes in 24 hr.	Several toes on each foot	Sulfaguanidine and penicillin; some cortical extract on 3d day	Amputation of 3 toes on each foot; diagnosis: clinical
Severe pain in feet from onset	Both feet, 5th fingers and distal portion of both thumbs	Massive from onset with sulfadiazine, penicillin and cortical extract	All arterial pulsations absent in feet shortly after onset; reappeared 8 hr. later; amputation of both legs and 5th finger of left hand
"Intense cyanosis of both feet" on admission; gangrene several days later	Both feet	Some penicillin prior to hospitalization; sulfadiazine and penicillin	Meningitis epidemic in area; gram-negative diplococci on smears from ocular discharge; both feet disarticulated
N. d.; gangrene obvious after 10 days in hospital	All toes bilaterally; tip of right index finger	Presumably sulfadiazine and penicillin	.....
N. d.	"Entire toes"	Penicillin and sulfonamide	Amputation of toes
"Pains in legs and difficulty in walking" 12 hr. after onset; both feet "black" 48 hr. after onset	Both feet; distal phalanges of right index and middle fingers	Sulfadiazine, cortin, penicillin, blood transfusions, etc., 24 hr. after onset	Amputation of both legs; bilateral ulnar nerve involvement; reputed response of blood pressure to cortin
Pain in feet at onset; feet "cold blue" within 24 hr.	"Most of toes"	Sulfadiazine and penicillin within day of onset	Dorsalis pedis arteries not felt; amputation of toes
N. d.; "toes of both extremities black and cold" on 12th day	Toes and soles both feet	Sulfadiazine, penicillin, blood transfusions and desoxycorticosterone 24 hr. after onset	Amputation of lower ⅓ both legs
Excruciating pain in both feet at onset; gangrene of toes definite 5 days after onset	All toes of left foot	Some penicillin prior to hospitalization; intensive sulfadiazine and penicillin therapy 36 hr. after onset	Amputation of lower ⅓ left leg; ECG changes marked; all arterial pulses of feet felt on admission

Severity of Illness.—In every report to date in which such data were available, the patients were gravely ill. In fact, it seems highly likely that most, if not all, of these patients would have died without the intensive treatment they received. Elliott and Kaye's patient—a possible exception—had the added complication of probable frostbite.

13. Branham, S. E.: Meningococcus (Neisseria Intracellularis), Bact. Rev. **4**:59-96 (June) 1940.

The condition of these patients appears to fit Herrick's [14] apt and often quoted description, "No other infection so quickly slays." It is not unreasonable to assume that gangrene of the extremities occurs, when it does occur, only in severe or fulminating meningococcic infections, if the patient survives. The advent of the sulfonamides and antibiotics in recent years coincides with the increase in published reports. One may, therefore, expect new cases to occur, despite intensive antibiotic treatment that will succeed in saving patients' lives but not always their limbs.

Gangrene of Skin.—Gangrene of the skin, by itself an infrequent complication of severe meningococcic infection,[15] was noted coincidentally with gangrene of extremities in all cases in which data were available. Generally, it was extensive. This association appears to be significant, since the main tissue of the hands and feet is skin, and the pathological process is probably the same. The histological studies of many authors,[16] especially those of Hill and Kinney,[1e] add considerably to understanding of the condition. These authors [1e] studied early to late skin lesions in 25 patients who came to autopsy. The initial factor, they observed, is localization of meningococci in the endothelial cells of the vessel walls. In rapid succession there are endothelial damage, inflammation of the vessel walls, necrosis and thrombosis and extravasation of blood. They pointed out that thrombus formation in cutaneous vessels has not been sufficiently emphasized. This thrombus formation is invariable in extensive lesions and may progress in spite of penicillin and sulfonamide treatment.

Gangrene of Extremities.—Gangrene of the extremities may be extensive but involves chiefly the toes and fingers, which, as stated above, have skin as their principal tissue. The toes were involved in all 12 cases analyzed; the fingers were affected only slightly in four cases, cases 1, 5, 7 and 9 (table). There was symmetrical involvement in all. The present patient clearly had identical involvement of both feet, but that of the right stopped short of gangrene. Most striking, although the records were incomplete, was the severe to excruciating pain in the feet at the onset of the illness (cases 1, 5, 7 and 9). The accounts distinctly separated this pain from the usual generalized aches and pains accompanying such a severe infection. It is also worth noting that in practically all these patients the gangrene progressed relentlessly in spite of the intensive treatment and coincidental clinical improvement. The

14. Herrick, W. W.: Extrameningeal Meningococcus Infections, Arch. Int. Med. **23**:409-418 (April) 1919.

15. Hill and Kinney.[1e] Dopter.[4] Thomas.[6]

16. Dopter.[4] Marie, J.; Seringe, P.; Cousin, M., and Marie, S. J.: Le purpura gangréneux meningococcique, Semaine d. hôp. Paris **22**:326-338 (Feb. 28) 1946.

evidence available did not incriminate the larger arteries, except late in the process when secondary thrombosis may occur. Where noted, pulsations in the dorsalis pedis, posterior tibial and peroneal arteries were usually present. An interesting exception was the patient of Smith and his associates [1c] who was seen relatively early, 10 hours after an abrupt onset, and had no pulsations over the dorsalis pedis, posterior tibial and radial arteries. Eight hours after admission to the hospital the pulsations reappeared but were "of small volume," and 11 hours after the patient's admission their volume was normal.

It becomes obvious in the interpretation of the above analysis that many factors are probably operative in precipitating this gangrene. At present, the following factors, some admittedly speculative, seem eligible for consideration: meningococcemia, shock, adrenal insufficiency, increased agglutinability or sludging of the blood, arterial spasm and toxins.

As stated, the evidence is strong that there is always an overwhelming bacteremia. In the case of Smith and his collaborators [1c] meningococci were revealed on direct blood smear. If the organisms are abundant enough, they may conceivably act as nuclei for the formation of thrombi in the small arterioles. The latter process may be hastened or augmented in some instances by the decrease in peripheral blood flow and the dehydration associated with clinical shock. Many of these patients had low blood pressure and peripheral vascular collapse. However, others did not. Not all peripheral vascular insufficiency is definable as shock. In Ebert and Stead's studies [17] conclusions were reached that circulatory failure caused by acute infections differed from ordinary failure. They failed to show significant hemoconcentration, decreased blood volume and increased venous pressure, nor was there any improvement in the circulation following transfusions of plasma, blood or dextrose solution.

Similarly, the importance of adrenal insufficiency in the production of the shocklike picture—the so-called Waterhouse-Friderichsen syndrome—remains, despite popular acceptance, to be proved. Thomas and Leiphart,[18] as well as others,[19] have registered the main objections to the concept: 1. Many patients with this syndrome have intact adrenal

17. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, J. Clin. Investigation **20**:671-679 (Nov.) 1941.

18. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in the Adult (Waterhouse-Friderichsen Syndrome): A Discussion of the Role Played by the Adrenal Gland in the Production of the Syndrome; Report of Two Adult Cases, J. A. M. A. **125**:884-890 (July 29) 1944.

19. (*a*) Kinsman and others.[8] (*b*) Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948, p. 1095. (*c*) Hoops, H. C., in Anderson,[19b] p. 219.

glands at autopsy (see also reports of Martland [20] and Daniels [21]). 2. The peripheral vascular collapse is more rapid than after experimental adrenalectomy in the dog. 3. Recovery, when it occurs, is more rapid than with adrenal regeneration. No clearcut evidence exists, to my knowledge, that adrenal cortex extract is effective in the treatment of these patients, although its use continues to be advocated.[22] Daniels said,[10] "Though the evidence is against adrenal insufficiency as a cause for shock, few have been willing to discard the use of adrenal cortex extract." In contradistinction, intensive antibiotic therapy alone has been widely successful in combating both the shock and the sepsis.

Factors increasing the agglutinability of the blood may precipitate or predispose to intravascular thrombosis. Cold hemagglutinins, of diagnostic help in primary atypical pneumonia, are also found in low, but frequently significant, titers in a wide variety of diseases.[23] Stats and Bullowa [24] and Bateman [25] have indeed reported peripheral gangrene clinically indistinguishable from the gangrene discussed in this paper. The gangrene was dry and limited to the digits, and pulsations were present in the larger arteries. In the present case, however, no cold hemagglutinins were demonstrated.

Knisely's [26] careful and extensive studies have demonstrated that most disease processes produce varying agglutinative or sludging phenomena in the red blood cells. This process, in Knisely's opinion, by slowing and blocking the circulation in the smaller vessels, may do considerable damage to the tissues. The extent of this damage has yet to be determined, but it may play some auxiliary role.

Arterial and arteriolar spasm may also be causally involved in the gangrene. The data, however, were scanty and chiefly indirect. In one

20. Martland, H. S.: Fulminating Meningococcic Infection with Bilateral Massive Adrenal Hemorrhage (the Waterhouse-Friderichsen Syndrome): With Special Reference to the Pathology, the Medicolegal Aspects, and the Incidence in Adults, Arch. Path. **37**:147-158 (Feb.) 1944.

21. Daniels, W. B.: Cause of Death in Meningococcic Infection: Analysis of 300 Fatal Cases, Am. J. Med. **8**:468-473 (April) 1950.

22. Thorn, G. W.; Forsham, P. H., and Emerson, K., Jr.: The Diagnosis and Treatment of Adrenal Insufficiency, Publication no. 29, American Lecture Series in Endocrinology, ed. by W. O. Thompson, Springfield, Ill., Charles C Thomas, Publisher, 1949, p. 97. Soffer, L. J.: Diseases of the Adrenals, ed. 2, Philadelphia, Lea & Febiger, 1948, p. 145.

23. Young, L. E.: The Clinical Significance of Cold Hemagglutinins, Am. J. M. Sc. **211**:23-39 (Jan.) 1946.

24. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities: Report of a Case, Arch. Int. Med. **72**: 506-517 (Oct.) 1943.

25. Bateman, J. C.: Symptoms Attributable to Cold Hemagglutination: Report of 2 Cases, Arch. Int. Med. **84**:523-531 (Oct.) 1949.

26. Knisely, M. H.; Block, E. H.; Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**:431-440 (Nov. 7) 1947.

of the 12 cases mentioned above,[1c] pulsations in the main peripheral arteries were at first absent and gradually reappeared. The severe pain at the onset is suggestive of arterial spasm. In the early phases of shock there is definite arterial and arteriolar vasoconstriction.[27] The roughly symmetrical distribution of the gangrene is again consistent with, though not conclusive of, arterial spasm. Abramson [28] has emphasized that the lower extremities normally have a greater degree of constrictor tone than the upper. This may possibly explain the more extensive gangrene in the lower extremities.

The meningococcus has an endotoxin and probably an exotoxin.[29] How do these toxins affect the peripheral vessels? Hill and Kinney's [1e] data indicated a direct localization in the endothelial cells, going on to inflammation, thrombosis and necrosis. These lesions bore a remarkable similarity pathologically to the phenomenon described by Shwartzman.[30] Shwartzman and Gerber [31] were of the view that this phenomenon, in both its specific and nonspecific form, may be an etiological factor in many infectious diseases manifesting local or generalized hemorrhagic-necrotic lesions. Black-Schaffer [32] also was of the opinion that it is highly probable that the hemorrhagic manifestations of meningococcic infection are due to the Shwartzman phenomenon and has produced such lesions experimentally in the rabbit.[33]

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27. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: The Peripheral Blood Flow in Surgical Shock: The Reduction in Circulation Through the Hand Resulting from Pain, Fear, Cold, and Asphyxia, with Quantitative Measurements of the Volume Flow of Blood in Clinical Cases of Surgical Shock, J. Clin. Investigation **15**:651-664 (Nov.) 1936. Richards, D. W., Jr.: The Effects of Hemorrhage on Circulation, Ann. New York Acad. Sc. **49**:534-541 (May 11) 1948. Lauson, H. D.; Bradley, S. E., and Cournand, A.: The Renal Circulation in Shock, J. Clin. Investigation **23**:381-402 (May) 1944. Davis, H. A.: Shock and Allied Forms of Failure of the Circulation, New York, Grune & Stratton, Inc., 1949, p. 79 ff.

28. Abramson, D. I.: Vascular Responses in the Extremities of Man in Health and Disease, Chicago, University of Chicago Press, 1944, p. 24.

29. Schoenbach, E. B.: The Meningococci, in Dubos, R. J.: Bacterial and Mycotic Infections of Man, Philadelphia, J. B. Lippincott Company, 1948.

30. Shwartzman, G.: Phenomenon of Local Tissue Reactivity, and Its Immunological, Pathological, and Clinical Significance, New York, Paul B. Hoeber, Inc., 1937.

31. Shwartzman, G., and Gerber, I. E.: Hemorrhagic Manifestations of Bacterial and Virus Infections: Experimental Studies and Pathological Interpretations, Ann. New York Acad. Sc. **49**:627-640 (May 11) 1948.

32. Black-Schaffer, B.: The Clinical Implications of the Shwartzman Phenomenon, J. Mt. Sinai Hosp. **16**:207-1213 (Nov.-Dec.) 1949.

33. Black-Schaffer, B.; Hiebert, T. G., and Kerby, G. P.: Experimental Study of Purpuric Meningococcemia in Relation to the Shwartzman Phenomenon, with Discussion of Mehingococcic Purpura, the Waterhouse-Friderichsen Syndrome and Bilateral Renal Cortical Necrosis, Arch. Path. **43**:28-54 (Jan.) 1947.

It is not possible, at this time, to implicate definitively any of the above discussed factors, or others not mentioned, or any combination of them. New cases of meningococcic infection with a complicating peripheral gangrene will doubtless be reported. If this complication is to be eliminated, it must first be understood.

SUMMARY

A case is reported of a 23 year old Negro man with meningococcemia and meningitis, complicated by gangrene of the left foot, eventually necessitating amputation. Only 11 other similar cases have been found in the literature. Nine of these have been reported since 1944.

An analysis of these reported cases suggests that (*a*) severe meningococcemia is always present, (*b*) the recent occurrence of this complication coincides with the advent of antibiotics, (*c*) it is uninfluenced by sulfonamide and antibiotic treatment and (*d*) gangrene of the toes and fingers is probably a special instance of the regularly associated gangrene of the skin.

The possible mechanism of this gangrene is discussed.

PROGRESS NOTES ON FIFTY DIABETIC PATIENTS FOLLOWED TWENTY-FIVE OR MORE YEARS

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FOREWORD

Between 1922 and 1929 in all our fatal cases of diabetes the average duration of life after onset was eight years. It ranged from 2.8 years for patients under 10 years of age to 9.5 years for those with onset between 40 and 59 years. Arteriosclerosis was even then recognized as important, and, therefore, we welcomed a study by Dr. H. C. Shepardson of this feature, especially in a series of 50 patients with onset under 40 years of age, who already had had diabetes five or more years, hoping that the eventual course of these patients could be followed and would disclose useful information.

Below, Dr. Ruth Reuting has summarized the present status of this group. Not only did the patients in the series who died live more than twice as long, but the surviving patients lived more than three times as long as the average duration in all our cases of fatal diabetes up to 1930. Nevertheless, the outlook for the diabetic after 25 years of diabetes is serious, although far more hopeful than often reported.

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PRESENT STATUS OF SERIES

A GROUP of 50 patients whose diabetes mellitus began prior to 1924 has been traced for over 25 years, and a progress report to Nov. 1, 1949 is presented.

The group has been known as the "Shepardson cases," inasmuch as the patients were originally selected for study by Dr. H. Clare Shepardson in 1929, at which time it was desired to make an investigation of possible etiological factors concerned in the vascular complications of diabetes. Patients were chosen at random, provided they had had diabetes for more than five years and were under 40 years of age. Shepardson's findings were published in May 1930.[1]

This study was aided by a grant from the Life Insurance Medical Research Fund.

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1. Shepardson, H. C.: Arteriosclerosis in the Young Diabetic Patient, Arch. Int. Med. **45**:674 (May) 1930.

Living Patients.—Thirty-one of the 50 patients survive. Their average age is now 44.8 years and the average duration of their disease 28.4 years, thus emphasizing the prolonged period of care diabetes with onset under 35 years of age entails. Of the living patients one acquired diabetes in 1918, five in 1919, six in 1920, five in 1921, ten in 1922 and four in 1923. Thirty of the 31 surviving patients are active and carry ordinary responsibilities; the remaining patient has been incapacitated by a neurosis. The group includes two lawyers, two clergymen, a physician, a newspaper reporter, a photographer, a bank president and seven housewives, two of whom do secretarial work in addition to housekeeping. One patient, case 2353, a woman 37.1 years of age with diabetes of 28.3 years' duration, has a 9 month old baby, delivered by cesarean section after an uneventful pregnancy. Another, a man 35.7 years of age (case 1616) with diabetes of 30.3 years' duration, reported by letter that his wife had recently given birth to twins. A woman 41 years old (case 2617) was awarded a Quarter Century Victory Medal in 1948 for having survived 25 (actually 26) years of diabetes without demonstrable evidence of vascular sclerosis, after thorough examination by an internist, rōentgenologist and ophthalmologist.

Deaths.—Nineteen, 38 per cent, of the 50 patients are dead. Their average age at the time of death was 34.9 years and the average duration of diabetes 17.6 years. The causes of death in individual patients are listed in table 1, and the percentages due to various causes are summarized in table 2.

Cardiovascular-renal disease heads the list of causes of death, having claimed seven persons. Tuberculosis and nontuberculous infection caused death in four patients each. One patient died of diabetic coma,[2] and three died of causes unrelated to diabetes (viz., pulmonary embolism following appendectomy, case 2528, automobile accident, case 2661, and neuromyelitis optica, case 6416).

Complications.—On consideration of the group of 50 patients as a whole, it is impressive to note that there have been seven cases of pulmonary tuberculosis among them—an incidence of 14 per cent. Four patients (cases 2448, 4232, 3332 and 4743) died of this disease. In a fifth patient (case 3062), in whom death was due to coronary occlusion, tuberculosis of the upper lobe of the right lung was discovered at autopsy. (Physical examination and roentgen study had failed to demonstrate this lesion, which, nevertheless, showed caseation, with microscopic evi-

2. Another patient, case 6359, was also admitted to the hospital in diabetic coma, but acidosis was corrected eight days before death. Death was actually due to severe renal infection. One patient, case 2448, died in diabetic coma, which was superimposed on overwhelming tuberculosis. Therefore, coma was implicated in three deaths, though a secondary factor in two.

dence of tuberculosis.) Two patients whose tuberculosis is classified as "arrested" are living useful lives at present.

Carcinoma has been present in two patients (cases 436 and 3852), affecting the colon in both. The former patient died in 1944, two years

TABLE 1.—*Causes of Death in Individual Cases, Shepardson Series, 1930 to November 1949*

Case No. (Joslin)	Sex	Date of Death	Age at Death, Yr.	Duration of Diabetes, Yr.	Cause of Death
436	F	8-12-44	55.5	35.3	Cerebral thrombosis
1469	F	9- 9-48	41.4	30.7	Hypertensive cardiovascular disease with myocardial infarction
1609	M	7-25-35	28.7	16.2	Carbuncle; cellulitis; septicemia
2005	F	2-21-31	42.3	12.4	Chronic nephritis; acute cardiac failure
2008	M	9-24-38	46.9	17.9	Perinephric abscess with septicemia
2448	M	2-20-28	24.1	6.2	Pulmonary tuberculosis
2528	F	6- 3-37	25.9	16.5	Pulmonary embolism following appendectomy
2661	M	3-19-45	28.7	23.5	Automobile accident
2967	M	9-20-35	42.3	13.3	Diabetic coma
3062	F	6-22-42	51.0	20.0	Coronary occlusion
3078	F	3- 3-34	23.5	11.2	Pneumococcic meningitis (right mastoiditis); chronic otitis media; bilateral pyelonephritis
3332	M	3-23-42	36.6	19.2	Pulmonary tuberculosis
3353	M	12-25-44	32.6	22.1	Coronary thrombosis; hypertension and hypertensive cardiovascular disease
3620	M	4-18-32	20.7	8.7	Chronic nephritis
4232	F	11-25-36	29.3	15.2	Pulmonary tuberculosis
4743	F	5-25-36	27.9	13.2	Pulmonary tuberculosis
6359	F	2-25-36	31.8	13.5	Pyonephrosis
6416	M	1-29-47	33.2	24.7	Neuromyelitis optica
6717	F	2- 6-31	40.6	15.1	Chronic nephritis; acute cardiac failure

TABLE 2.—*Causes of Death in Shepardson Series, 1930 to November 1949*

Causes of Death	No. of Deaths	Per Cent of 50 Cases	Per Cent of 19 Deaths
Cardiovascular-renal disease..... Coronary occlusion (3) Cerebral thrombosis (1) Chronic nephritis (3)	7	14	36.8
Pulmonary tuberculosis	4	8	21.0
Nontuberculous bacterial infection.....	4	8	21.0
Coma	1	2	5.3
Miscellaneous (unrelated to diabetes)....	3	6	15.9
	19	38	100.0

after bowel resection. Permission for autopsy was not obtained, and death was assumed to be due to cerebral thrombosis. (A possible metastatic lesion was considered by the physician who attended the patient at the time of death.) The other patient (case 3852) has had no recurrence of her lesion 11 years after bowel resection in 1938. In 1948, at the age of 58, she suffered a coronary occlusion but, with adequate rest and standard therapy, made a good recovery. In spite of

this episode and against advice, she recently embarked on a 2,400 mile (3,864 km.) motor trip with enthusiasm and returned without untoward incident.

Gangrene has not occurred in any patient. Osteomyelitis has developed twice, leading to amputation of a toe in one person and a partial finger amputation in another.

Of 31 living persons, 18 exhibited retinopathy in some degree; 11 were reported by their physicians as having normal fundi, and in two patients (not seen by us) examination was not made. Blindness due to retinopathy has not occurred, and there have been no mature cataracts. Early lenticular opacities have been noted in four persons.

Twenty-seven of the 31 living patients showed arterial calcification by roentgen examination. Two patients (cases 2617 and 2560) examined in 1947 and 1949, respectively, had no evidence of vascular calcification.

Eight of the 31 persons displayed azotemia of moderate degree, as evidenced by blood nonprotein nitrogen levels between 40 and 50 mg. per 100 ml. Proteinuria of more than 20 mg. per 100 ml. was noted in nine of the 31 living patients and in five of them exceeded 100 mg. per 100 ml. in a single determination. Data are not available on two patients.

Plasma cholesterol levels varied between 148 and 470 mg. per 100 ml., with an average of 224 mg. per 100 ml. for the 29 patients examined. Oddly enough, the lowest single value was that in case 5433. This patient has shown a marked degree of vascular calcification for at least eight years. The highest value was that in case 1616. Recent roentgen reports are not available in this case, and geographic distance has prevented complete study. A blood nonprotein nitrogen determination in 1949 was reported as 45 mg. per 100 ml., but the patient apparently has had no symptoms of illness, and the birth of his fourth child occurred this year. (In this case the most recent roentgen reports available are dated 1940, at which time no vascular calcification was noted about the ankle joints, the only part examined.)

A recent blood pressure reading is available for 28 of the 31 living patients. In 15 of these persons the blood pressure was not over 140/80. The systolic pressure was elevated above 140 mm. Hg in 13 patients and the diastolic pressure above 80 mm. in 13. The average pressure of the 28 patients was 142/83. The highest reading noted was 210/110, that of a woman 36.0 years of age (case 3778). This patient, when examined in October 1949, had not consulted a physician since August 1939. Pitting edema of the ankles and dyspnea on exertion had been present for nearly a year. Proteinuria to the extent of 300 mg. per 100 ml. was found in a single specimen, but the blood nonprotein nitrogen was not elevated (33 mg. per 100 ml.).

The significance of cardiovascular-renal disease is evident. It has been the cause of seven of the 19 deaths, or 37 per cent, or 14 per cent of the total group of 50 patients. Among the living patients ominous signs of hypertension, azotemia and proteinuria are evident in significant numbers (see above), and 27 of 29 living patients examined roentgenologically showed evidence of vascular calcification. Four patients (cases 1469, 2967, 3062 and 3078) came to autopsy at the New England Deaconess Hospital. Three displayed serious arteriosclerotic changes. In one, a woman (case 3062), "generalized arteriosclerosis" was described and death was due to coronary occlusion at the age of 51.0 years, with diabetes of 20.0 years' duration. Another woman (case 3078) died of pneumococcic meningitis (in 1934, before the advent of antibiotic therapy). Diagnoses at autopsy, in addition to meningitis, were (1) right mastoiditis, (2) bilateral chronic otitis media, (3) amyloidosis of kidneys and (4) atherosclerosis. Examination of the coronary arteries and aorta revealed "scattered atheromatous plaques." The patient had died at the age of 23.5 years, after 11.2 years of diabetes. The third woman (case 1469), who died at 41.4 years of age after 31 years of diabetes, showed "generalized arteriosclerosis, especially of coronary, cerebral and renal arteries." The description of microscopic study of the uterus in this case is interesting in view of the fact that the patient had had a pregnancy resulting in delivery of a normal child nine years previously. It states, "The myometrium is remarkably condensed and cellular and supplied by arteries involved by medial hyalinization and intimal thickening, the whole picture resembling that of the uterus of a 70 year old patient."

The mortality rate is high, 38 per cent, but one is tempted to think that with the methods of treating infections, including tuberculosis, available today, the number of deaths might have been decreased by eight cases, or 16 per cent. The death due to uncomplicated diabetic coma might well have been prevented, as treatment was not optimal. (The patient was moribund on admission to the hospital and died after one hour.) Three of the deaths were due to causes unrelated to diabetes. The remaining deaths, numbering seven, or 14 per cent, were due to cardiovascular-renal disease.

Cases with Onset in Childhood.—The onset of diabetes occurred before the fifteenth birthday in 26 of the 50 patients, or 52 per cent. Among the 19 patients who died, onset occurred before the fifteenth birthday in 10 (52.6 per cent of the deaths) and average duration of life after onset of diabetes was 18.2 years. Among the 31 living patients, onset occurred before the age of 15 years in 16 persons (51.6 per cent of the surviving number). The average age of this group is now 37.3 years and the average duration of diabetes 28.5 years.

Use of Insulin.—Thirty of the 31 living patients have taken insulin constantly for more than 20 years, and 25 of the 31 living patients began using insulin prior to 1925. One patient (case 2675) has taken insulin only at intervals during acute illnesses. She has omitted it at other times but stated that she has been extremely careful in her dietary regulation throughout the years and has remained aglycosuric.

Treatment.—Treatment has not been uniform. The group has become widely scattered geographically, and recent data have in many cases been obtained at a single examination or through cooperation of the patient's local physician. A single blood sugar determination cannot be considered an index to glycemic control over the past 20 years, and it seems best, therefore, to evaluate the results of treatment through study of other groups of patients who have been more constantly observed.

SUMMARY

The prolonged duration of life in this series after the onset of diabetes is impressive. Fifty patients with diabetes mellitus of five years' duration or more, whose age at onset was less than 40 years, were selected at random in 1929. Thirty-one of the group survive; their average age to Nov. 1, 1949 is 44.8 years and the duration of their diabetes 28.4 years. Nineteen of the group have died. (Causes of death are listed in table 1.) The average age at the time of death was 34.9 years and the duration of diabetes 17.6 years. The average duration of diabetes of the 50 patients, living and dead, is now 24.3 years.

Cardiovascular-renal disease has been the most significant cause of death. Nephritis has claimed three patients, coronary occlusion three patients and cerebral thrombosis one patient.

Pulmonary tuberculosis has been prominent, occurring in seven patients, of whom two survive. This disease was the cause of death in four persons.

Nontuberculous bacterial infection has also been of grave significance and has claimed four patients. It is believed that if recent advances in biochemotherapy had been available to the patients who succumbed to infections their courses might have been significantly altered.

Uncomplicated diabetic coma has been the cause of death in one patient.

Carcinoma has occurred in two patients, affecting the colon in both instances, but has not been the cause of death in any patient.

Gangrene has not occurred. Osteomyelitis has developed twice, necessitating amputation of a toe in one person and partial finger amputation in another.

Retinopathy has been reported in 18 of 29 living patients examined. No instance of blindness has occurred, and there have been no mature

cataracts, though early lenticular opacities were reported in four of the living patients.

Arterial calcification has been demonstrated roentgenologically in 27 of 29 persons examined.

Proteinuria of more than 20 mg. per 100 ml. has been found in nine of the 31 living patients and in five exceeded 100 mg. per 100 ml. Eight of the living patients showed moderate azotemia, as evidenced by blood nonprotein nitrogen levels of 40 to 50 mg. per 100 ml. The systolic blood pressure was found to be elevated above 140 mm. Hg in 13 patients and the diastolic pressure above 80 mm. Hg in 13 patients.

A living child was born to one patient at the age of 36.4 years, after 27.6 years of diabetes, and the wife of one of the male patients gave birth to a normal child after his diabetes had existed 29.6 years.

The experience in tracing this group of patients is, on the whole, heartening. Although the mortality has been high, the surviving group, numbering 31 patients, or 62 per cent, are with one exception active persons, living useful lives.

ACTION OF ATROPINE ON THE CARDIOVASCULAR SYSTEM IN NORMAL PERSONS

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THE MAJORITY of clinical observations indicate that attacks of angina pectoris are prone to occur during the fourth, fifth and sixth decades, and that they are relatively infrequent either prior to or after this period. The symptoms of angina pectoris result when the blood supply to the heart muscle is inadequate for its needs at that moment. Gilbert,[1] in discussing vasomotor changes in the coronary arteries, called attention to the fact that this inadequate blood supply in many cases may be due completely, or in part, to anatomic changes in the vessels which render them unable to meet the increased demands that accompany the increased work of the heart, but he also stressed that a similar disproportion between the blood supply and demand will result if the vessels fail to increase in caliber in response to the increased needs, even though they may be anatomically intact. He stated that this same disproportion will result if the blood flow through the coronary arteries is diminished in consequence of a vasoconstricting action. He was able to demonstrate that an increase of vagal tone is coincident with increase in age and that this increase is a function of age alone and not of pathological changes in the heart.[2] Rein,[3] in discussing vasomotor factors of the coronary arteries, stated that a failure of relaxation from the vagal tone can result in an actual vasoconstriction when there is a lack of equilibrium between the supply of blood for the myocardium and the demand. McEachern,

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† Dr. C. F. G. Brown, under whose direction the collection of material and data in this manuscript was initiated, died May 29, 1950.

1. Gilbert, N. C.: Vasomotor Changes in the Coronary Arteries and Their Possible Significance, J. A. M. A. **113**:1925-1927 (Nov. 25) 1939.

2. Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, Arch. Int. Med. **31**:423-432 (March) 1923.

3. Rein, H.: Die Physiologie der Herz-Kranz-Gefässe: I. Mitteilung, Ztschr. f. Biol. **92**:101-114 (Nov. 30) 1931.

Manning and Hall,[4] in studying mortality rates following the experimental ligation of various arteries, concluded that a reflex mechanism is involved in the ischemic area produced which initiates afferent impulses that, in turn, produce efferent vagal impulses, causing constriction of the medium-sized and smaller-sized coronary arteries. They also showed that by removal of the cardiosensory pathways the mortality rate is remarkably reduced after sudden and permanent occlusion of the larger branches of the left coronary artery in animals. LeRoy, Fenn and Gilbert [5] reported a similar effect on the mortality rate after experimental occlusion of a coronary artery with the use of atropine.

A number of investigators have reported observations on variations of vagal tone at different ages. Grollman and Slaughter [6] stated that the inhibitory fibers of the vagus are almost inactive at birth but the tone increases with age up to 24 to 35 years and from this time lessens. They further stated that atropine does not quicken the heart action in the newborn child but in persons up to about 30 years of age the acceleration increases with age. From this point onward it lessens until the heart rate is increased by only four to five beats per minute in patients between 80 and 90 years of age. Sollman [7] similarly stated that the vagal tone is greatest between 20 and 30 years, less in old age (after 50 years) and least in infancy, and that the response in heart rate varies accordingly.

Since these concepts are at variance with our clinical impressions, and also since some clinicians avoid the use of atropine following acute myocardial infarction, this work was done to obtain a more comprehensive and quantitative answer to the difference in response to atropine in the various age groups.

EXPERIMENTAL STUDIES

This report is concerned with the observations on the effects of atropine sulfate in 133 subjects of both sexes and various ages. The age distribution is given in the table. A complete clinical history was taken and careful physical and laboratory examinations were made in each case. Only those subjects were studied who were found normal according to these procedures.

4. McEachern, C. G.; Manning, G. W., and Hall, G. E.: Sudden Occlusion of Coronary Arteries Following Removal of Cardio-Sensory Pathways, Arch. Int. Med. **65**:661-670 (April) 1940. Manning, G. W.; McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, ibid. **64**:661-674 (Oct.) 1939.

5. LeRoy, G. V.; Fenn, G. K., and Gilbert, N. C.: The Influence of Xanthine Drugs and Atropine on the Mortality Rate After Experimental Occlusion of a Coronary Artery, Am. Heart J. **23**:637-643 (May) 1942.

6. Cushny, A. R.: Pharmacology and Therapeutics, revised by A. Grollman and D. Slaughter, ed. 13, Philadelphia, Lea & Febiger, 1947, p. 473.

7. Sollman, T. H.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 7, Philadelphia, W. B. Saunders Company, 1948, p. 316.

We were desirous of giving a sufficient quantity of atropine to produce a pronounced effect on the vagi. Gilchrist[8] stated that, from his review of the case reports in the literature, it would appear that not infrequently conclusions have been drawn from the effects obtained on the administration of too small a dose of atropine. Lewis and his colleagues[9] observed that in dogs a dose of 0.01 mg. of atropine sulfate per kilogram of body weight had a decided effect in weakening the inhibitory termination of the vagus, but that this dose must be increased to 0.02 or 0.04 mg. per kilogram before the effects of even weak peripheral stimulation are abolished. They noted that in order to render strong vagal stimulation ineffective the dose had to be increased to 0.05 to 0.10 mg. per kilogram of body weight. From similar observations on man, they came to the conclusion that 1.0 mg. of atropine sulfate given by intravenous injections was sufficient to produce decided effects on the heart and near paralysis of the vagi. In order to produce complete paralysis in man, a dose of 3.0 to 6.0 mg. was required.

On the basis of the above observations, our subjects were given 0.02 mg. of atropine sulfate U. S. P. per kilogram of body weight. The solution was freshly

Number of Normal Subjects Studied in Various Age Groups

Age Range, Yr.	No. of Subjects
3 to 9	12
10 to 19	21
20 to 29	15
30 to 39	19
40 to 49	22
50 to 59	20
60 to 69	13
70 to 79	6
80 to 89	5
Total	133

prepared in distilled water without heat and was administered either intravenously or subcutaneously.

The subjects were studied in the afternoon after a light lunch. They were allowed to lie comfortably on a cot prior to receiving the atropine. During this control period electrocardiographic tracings, as well as frequent determinations of blood pressure, salivary flow and oral and skin temperatures, were made. It was found that at the end of this period that patients had all attained a basal state. The atropine was then administered without disturbing the patient, and the changes were noted. The heart rate was determined from the electrocardiographic tracings, which were taken at intervals of 4, 8, 12, 20, 30, 40, 50 and 60 minutes. Ninety-eight of the subjects received the atropine sulfate intravenously and 35 subcutaneously.

EFFECTS ON HEART RATE

All subjects showed an initial drop in heart rate and a subsequent rise following the administration of atropine. The heart rate was reduced for 15 to 30 seconds when the drug was given by the intravenous method

8. Gilchrist, A. R.: The Action of Atropine in Complete Heart Block, Quart. J. Med. **2**:483-498 (Oct.) 1933.

9. Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Atropine and Strophanthin, Heart **9**:21-53 (Dec.) 1921.

(not shown on the graph) and for about 10 to 15 minutes when it was given by the subcutaneous route. The change in heart rate observed was abrupt and greater with the intravenous administration and relatively slow but well marked with the subcutaneous injections. The heart rates of subjects given intravenous injections tended to return to normal more promptly than did the rates of those given subcutaneous injections. Figure 1 shows the effect on heart rate of the administration of atropine sulfate by the intravenous and subcutaneous methods. The curves illustrated in this figure are a mathematical composite combining the graphs of all subjects in each decade. Individual variations, therefore, are not

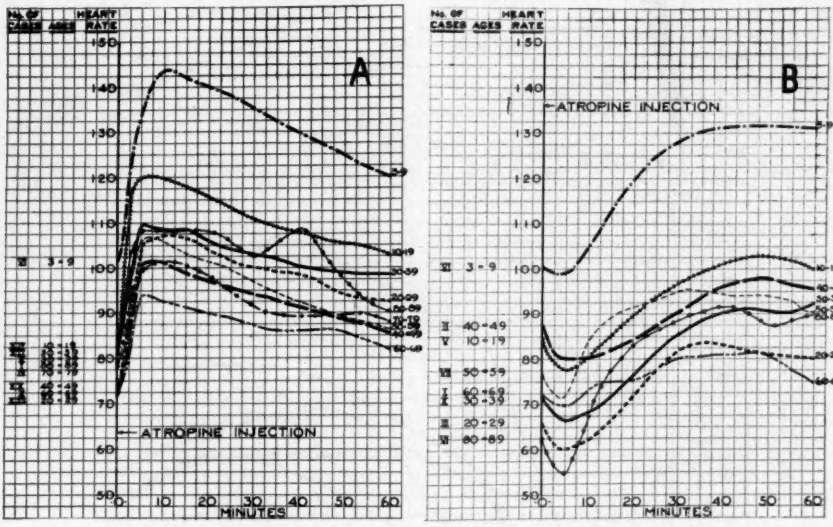

Fig. 1.—Composite graphs illustrating the effect of atropine sulfate on the heart rate when given intravenously (*A*) and subcutaneously (*B*) to subjects arranged in age groups of 10 year intervals.

apparent. It is to be noted in these graphs that there was a decided effect on heart rate in response to the atropine given and that this response was most pronounced in persons in the first two decades of life. This is contrary to the observations of earlier investigators. The initial fall in heart rate in those subjects receiving atropine sulfate subcutaneously is apparent when compared with the less marked and short-lived response of those receiving atropine intravenously. An analysis of these curves indicates that those subjects in the first and ninth decades given atropine subcutaneously showed the greatest response in percentage change in

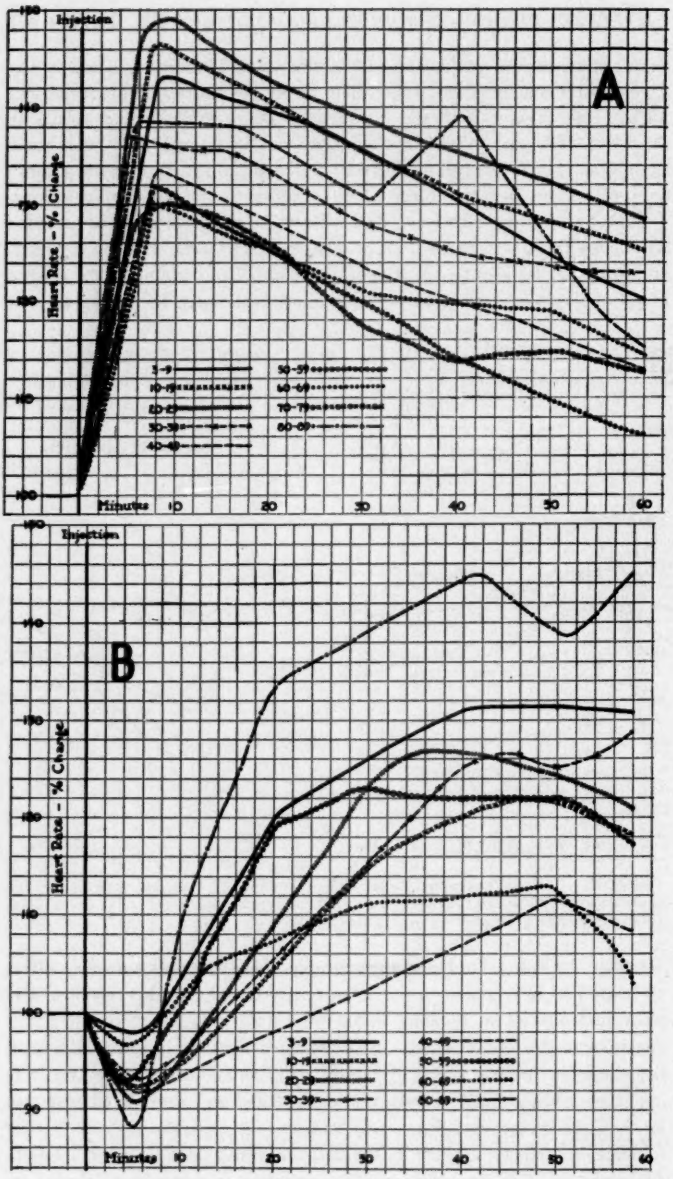

Fig. 2.—Tracings illustrating the percentage change in heart rate in various age groups when atropine sulfate is given intravenously (*A*) or subcutaneously (*B*).

heart rate, while those in the fifth decade showed the least response. Subjects in the other decades had intermediate responses. When atropine was given intravenously, the greatest percentage change in heart rate was experienced in members of the first three decades, whereas those in the fifth, sixth and seventh decades showed a lesser percentage change. Figure 2 illustrates the percentage change in heart rate discussed.

When the 133 individual graphic records of heart rates were studied, it was noted that, in addition to age differences, the strong, sturdy persons had a characteristic reaction and the tall, thin, asthenic subjects had another reaction. The sthenic group was resistant to the dosage

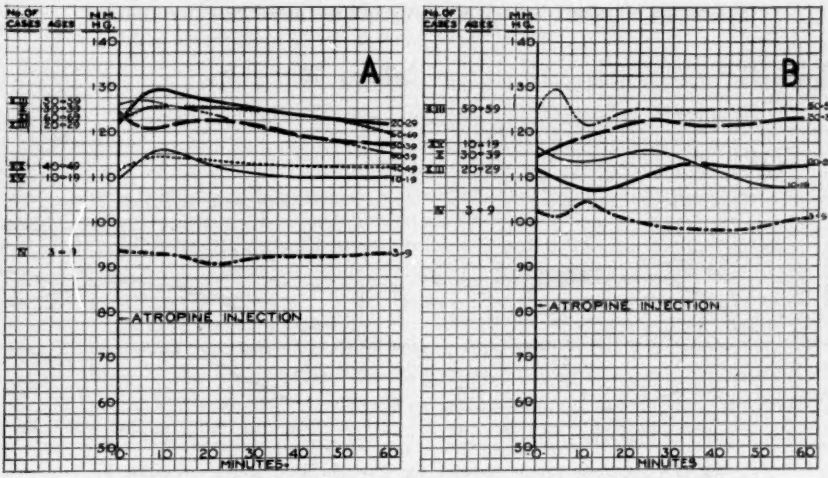

Fig. 3.—Composite graphs showing the systolic blood pressure response by decades to intravenously (*A*) and subcutaneously (*B*) administered atropine sulfate.

of drug given, whereas the asthenic group showed a pronounced drug effect. The heart rates of average persons produced a curve which was approximately a mathematical mean of the rates of the aforementioned two groups.

EFFECTS ON BLOOD PRESSURE

Blood pressure determinations were made with a wall model mercury manometer at the intervals mentioned previously. The blood pressure changes occurring in normal persons after atropine administration showed large individual differences. The same person, however, displayed his or her characteristic reaction when the experiment was repeated several times. One subject was studied on five different occasions over

a period of months and always showed the same type of blood pressure reaction. In general, it was noted that the blood pressure response after the administration of atropine was more brisk in subjects ranging from 20 to 50 years of age. Before the age of 20 and after the age of 55, a much greater stability of blood pressure existed. The blood pressure curves varied greatly according to the mode of administration of the atropine. Figures 3 and 4 illustrate the systolic and diastolic blood pressure responses following the intravenous and the subcutaneous administration of atropine sulfate.

After atropine was given intravenously, the systolic and diastolic blood pressure curves showed an initial rise for the first 15 to 20 minutes, followed by a gradual fall which approached the initial pressure. Blood

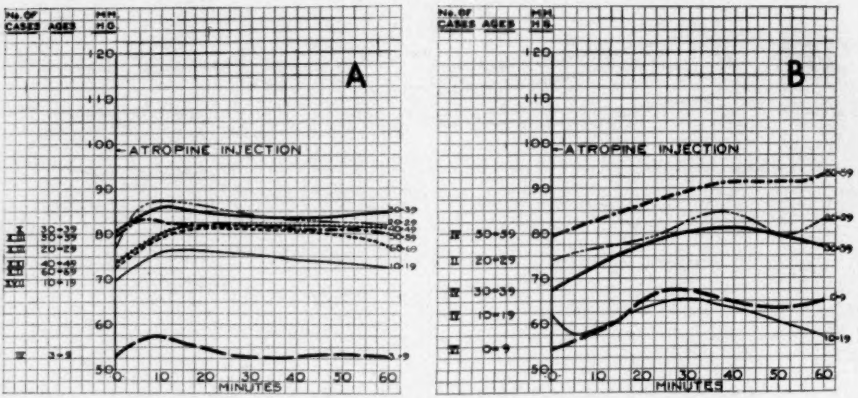

Fig. 4.—Composite graphs showing the diastolic blood pressure response by decades to intravenously (*A*) and subcutaneously (*B*) administered atropine sulfate.

pressure curves obtained after the subcutaneous administration of atropine were, however, less consistent. The mathematical composite curves plotted from the latter records resulted in a nearly straight line due to cancellation. On consideration of the effect of atropine on the entire group, the systolic pressures were noted either to increase or to decrease, whereas the diastolic pressures almost invariably increased. If the generally accepted idea is true, that the diastolic blood pressure is due to resistance in small blood vessels, then it must be concluded that atropine increases this resistance.

It was of interest to note that with the appearance of the flush following the administration of atropine the pulse pressure was usually diminished. In the majority of the subjects studied, this was observed

to be due to the increase in diastolic pressure rather than to a fall in systolic pressure. As stated above, in some cases the systolic pressure did fall, but the pulse pressure was diminished owing to a disproportionate rise in diastolic pressure. There was an apparent increase in the vascular tone in the systemic circulation, and the decrease which might be anticipated from previous work was not seen.

EFFECTS ON ELECTROCARDIOGRAPHIC TRACINGS

Electrocardiographic tracings made on these subjects showed no change following the intravenous or subcutaneous administration of atropine, other than the changes in heart rate mentioned above and some small changes in voltage of the QRS complexes. This is in accordance with the observations of Levin [10] and Schennetten.[11]

EFFECTS ON ORAL AND SKIN TEMPERATURES

It was noted that after the intravenous administration of atropine there was usually a drop in the oral temperature. Measurements were made with a 30 second certified Tycos thermometer. The initial temperatures were consistently higher in younger subjects and decreased with age. Persons in all decades showed only a slight difference in temperature drop within the various age groups. The oral temperatures observed after the subcutaneous administration of atropine sulfate exhibited no consistent change.

Skin temperatures were obtained with the use of a thermocouple. It was found that there was a consistent upward trend in the skin temperatures during the flush. This was invariably followed by a rapid fall in one to four minutes.

EFFECTS ON SALIVARY SECRETION

The salivary secretion was determined by measuring the weight of saliva absorbed by a dental cotton roll placed in the mouth. Observations were made during the control period and at the intervals stated above.

It was seen that the salivary flow of subjects up to the age of 20 was less affected by atropine than that of subjects in the older age groups. The secretory flow in the younger subjects did not drop to as low a level as in the older persons and recovered much more rapidly.

During the first 15 minutes after the subcutaneous administration of atropine, there was a definite stimulation phase in the flow of saliva in subjects of the groups from 10 to 30 years of age.

10. Levin, E.: Immediate Effects of Intravenous Atropine on Cardiac Rhythm, Rev. argent. de cardiol. **6**:353-373 (Jan.-Feb.) 1940.

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COMMENT

Atropine has varying effects on the heart rate, depending on the age of the subject. The younger groups showed a sharper increase in rate after atropine administration, with a more rapid return to normal, than the older groups. If the degree of vagal tone can be measured by the changes in heart rate after atropine administration, then these results indicate that vagal tone is greatest in childhood and gradually decreases through the succeeding decades, except for the relative differences observed between the ages of 40 to 60. It is of interest to note that Wartman and Hellerstein,[12] in analyzing the incidence of myocardial infarction, showed that 62 per cent of the first infarctions occurred in the aforementioned age groups. Nay and Barnes,[13] as well as Barnum and his associates,[14] described a similar distribution incidence of myocardial infarction. Later in life, the inhibitory tone of the vagus again becomes more stable and consistently more active, as noted in the ninth decade group.

The subjects showed a great variability in blood pressure changes on atropine administration. The same person, however, displayed a characteristic reaction when the test was repeated on different occasions. The subjects below the age of 20 and over the age of 55 showed less change in blood pressure reactions after the administration of atropine. The reactions in those from 20 to 55 were brisk, varying and unpredictable. The diastolic blood pressure usually rose after atropine was given and became more elevated in older persons.

In the opinion of some clinicians coronary heart disease is due entirely to arteriosclerotic changes. However, others consider that the element of spasm of the vessels plays a large role in the formation of coronary thrombosis. Potter,[15] after making many roentgen studies of normal persons and of patients with intermittent claudication, demonstrated that in the latter arteriosclerosis was not usually evident on roentgen examinations. On the other hand, he observed that patients with serious arteriosclerotic changes in the vessels of the extremities usually did not complain of claudication. It would be difficult to exclude either degenerative changes or spasm of the coronary vessels as a domi-

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nant factor in occlusions. Either could produce thrombosis, but more likely a combination of the two is responsible for the majority of myocardial infarctions.

The question of the efficacy of atropine sulfate in the treatment of myocardial accidents has been frequently raised. We have pointed out earlier the experiences of other investigators in reducing the mortality following experimental myocardial infarction with the use of atropine sulfate or its equivalent. Essex and his co-workers [16] in other experimental observations noted that if atropine sulfate was given in sufficient doses the blood flow in the left coronary artery was increased as much as 86 per cent and the flow was 25 per cent above the control level at the end of 49 minutes. This observation was reported earlier by Anrep and Segall,[17] Rein,[18] Narayana [19] and Anrep.[20]

Suarez and his associates [21] reported that when 1.0 mg. of atropine sulfate was given to eight normal subjects ranging from 17 to 60 years of age six showed an increase in the cardiac minute volume. These authors also observed that pulmonary ventilation and oxygen consumption increased slightly in the majority of the subjects.

CONCLUSIONS

We have measured the reactions of the vegetative nervous system to atropine and observed a greater individual variability in the threshold of nerve control among normal persons in the age groups showing the greatest incidence of coronary heart disease. These experiments lead us to believe that atropine sulfate should play a prominent role in the treatment of coronary thrombosis.

Dr. Stuart Cromer assisted in collection of data and preparation of this manuscript.

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17. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13**:239-260 (Sept.) 1926.

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20. Anrep, G. V.: Lane Medical Lectures: Studies in Cardiovascular Regulation, Stanford University, Calif., Stanford University Press, 1936.

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LIVER DYSFUNCTION FOLLOWING ABDOMINAL OPERATIONS

The Significance of Postoperative Hyperbilirubinemia

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SEVERAL reports in the literature deal with the effect of surgical operations on liver function.[1] The hippuric acid and sulfobromophthalein (bromsulphalein®) sodium tests have been used in several studies. Tagnon, Robbins and Nichols [2] reported changes in the sulfobromophthalein clearance following extra-abdominal operations. In their series of patients there was no consistent postoperative alteration in the thymol turbidity or cephalin flocculation reactions.

The work reported below describes the effect of abdominal operation on the sulfobromophthalein clearance, cephalin flocculation and thymol turbidity. Abnormalities of the two former reactions were observed in a high proportion of the cases reported here. In addition, since sulfobromophthalein clearance parallels bilirubin clearance in dogs,[3] an attempt was made to correlate the incidence of postoperative hyperbilirubinemia in this series of patients with the impairment of the sulfobromophthalein clearance.

MATERIAL AND METHODS

The observations were made on patients admitted to the surgical services at Memorial Hospital. The clinical and laboratory data were recorded and graded

From the Department of Medicine, Memorial Center, New York City.

1. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by Quick Hippuric Acid Test: III. Various Surgical States, Arch. Surg. **37**:443 (Sept.) 1938. Schmidt, C. R.; Unruh, R. T., and Chesky, V. E.: Clinical Studies of Liver Function: Effect of Anesthesia and Certain Surgical Procedures, Am. J. Surg. **57**:43, 1942.

2. Tagnon, H. J.; Robbins, G. F., and Nichols, M. P.: The Effect of Surgical Operations on the Bromsulfalein-Retention Test, New England J. Med. **238**:556, 1948.

3. Cantarow, A.; Wirts, C. W., Jr.; Snape, W. J., and Miller, L. L.: Excretion of Bilirubin and Bromsulfalein in Bile, Am. J. Physiol. **154**:211, 1948.

as outlined in a previous report,[2] with the exception of the sulfobromophthalein test, for which a 45 minute period was used, and of the cephalin flocculation test, for which a single 48 hour reading was recorded.

The cases presented here can be divided into two groups, group I consisting of 22 patients whom we followed personally and group II of 11 patients selected from 100 consecutive patients whose hospital charts were analyzed. All patients in both groups underwent major surgical operations, except one (case 21) who had a papilloma of the urinary bladder removed by electrocautery.

One patient (case 17) had had serum hepatitis 1½ years prior to surgical intervention and had an elevated bilirubin level on admission. One patient (case 33) had chronic cholecystitis, with no evidence of liver dysfunction. On their admission, nine patients had abnormal thymol turbidity reactions, four had abnormal cephalin flocculation determinations, four had elevated serum bilirubin levels and five had increased retention of sulfobromophthalein. Three patients (cases 1, 26 and 33) had mild diabetes not requiring insulin. One patient (case 10) had arteriosclerotic heart disease without failure preoperatively and postoperatively, graded 1A according to the New York Heart Association Classification. Two patients (cases 26 and 31) gave a history of syphilis but presented no clinical signs of the disease and had negative blood Mazzini reactions. All patients, except one (case 13), were afebrile on admission.

The over-all clinical picture is presented in table 1. All patients received preoperative medication in the form of morphine or merperidine (demerol®) hydrochloride, atropine and pentobarbital (nembutal®) calcium in the usual doses. Butethamine (monocaine®) formate was the drug used to produce spinal anesthesia; table 1 lists the other anesthetic agents given.

Preoperative and postoperative liver function tests were carried out at intervals of one or two days in all patients of group I. In group II results of such tests as were presented in the charts are reported.

Transfusions were with blood bank blood preserved in anticoagulant acid citrate dextrose solution for an average of seven to 10 days. After the operation, patients were given fluids parenterally in the form of 2,000 to 3,000 cc. of 5 per cent dextrose in isotonic sodium chloride solution as required. All patients received large daily amounts of vitamins of the B group in the form of betasynplex® and ascorbic acid representing several times the normal daily requirements. All preoperative liver function tests were done before the administration of blood. No evidence of hemolytic transfusion reaction was seen in any patient.

RESULTS

1. *Serum Bilirubin Level.*—Postoperatively, a rise in the serum bilirubin level of 0.3 mg. or more was observed in 19 patients. Five other patients (cases 23, 25, 26, 27 and 30), with no preoperative tests, had serum bilirubin levels of 1 mg. or more postoperatively. Therefore, 24 of 33 patients had significant or abnormal elevations in serum bilirubin postoperatively. The highest level of bilirubin was usually observed on the first postoperative day. One patient (case 26) had a level of 13.56 mg. on the sixth day after operation, which fell to normal by the thirtieth day.

The amount of blood used during the operative procedure ranged from none in one patient (case 12) to 6,000 cc. in two patients (cases 26 and 29). Fourteen patients received 2,000 cc. or more of whole

TABLE 1.—*Summary of Operative Data on Thirty-Three Patients Undergoing Major Abdominal Procedures*

Case No.	Age	Sex	Diagnosis	Operation	Anesthesia	Duration of Operation, Hr.	Fall in Blood Pressure*	Post-operative Fever†	Blood Administered, Cc.		Comment
									During Operation	Within 48 Hr.	
1	61	F	Carcinoma of rectum	Abdominoperineal	Gas,‡ oxygen, ether	4½	2+	0	1,500	.....	1,500 cc. blood preoperatively
2	59	F	Carcinoma of rectum	Abdominoperineal	Gas, oxygen, ether	2½	0	1+	500	.....	1,500 cc. blood preoperatively
3	69	F	Carcinoma of rectum	Abdominoperineal	Spinal and thiopental sodium	3½	3+	0	2,000	1,000	.....
4	50	F	Carcinoma of rectum	Abdominoperineal; hysterectomy	Spinal and thiopental sodium	4	3+	0	2,000	.....	2,000 cc. blood preoperatively
5	63	M	Carcinoma of rectum	Abdominoperineal	Spinal and thiopental sodium	3	0	1+	1,500	.....	.....
6	42	M	Carcinoma of rectum	Abdominoperineal	Spinal and thiopental sodium	3½	0	1+	1,500	.....	.....
7	63	M	Carcinoma of rectum	Abdominoperineal	Spinal	2½	0	0	1,000	.....	.....
8	38	F	Carcinoma of sigmoid	Resection and anastomosis; hysterectomy; partial cystectomy	Spinal	4	0	0	2,000	.....	1,500 cc. blood preoperatively
9	70	M	Carcinoma of sigmoid	Resection and anastomosis	Gas, oxygen, ether	2	0	0	1,000	.....	.....
10	77	F	Carcinoma of sigmoid	Resection and anastomosis	Spinal	2½	±	0	1,000	.....	.....
11	49	F	Carcinoma of sigmoid	Resection and anastomosis	Spinal	3	1+	1+	1,500	500	.....
12	66	M	Carcinoma of sigmoid	Transverse loop colostomy	Spinal	1	0	0	.....	.....	.....
13	39	F	Carcinoma of ascending colon	Resection and anastomosis	Gas, oxygen, ether	3½	0	3+	1,500	.....	5,500 cc. blood preoperatively; jaundice 4th day postoperatively
14	44	F	Carcinoma of cervix	Hysterectomy and node dissection	Gas, oxygen, ether	1½	0	0	1,000	.....	.....
15	37	F	Carcinoma of cervix	Hysterectomy and node dissection	Gas, oxygen, ether	1½	0	2+	500	500	.....
16	53	F	Carcinoma of cervix	Pelvic exenteration	Gas, oxygen, ether	3	0	0	3,000	.....	.....
17	51	F	Carcinoma of cervix	Pelvic exenteration	Gas, oxygen, ether	4	3+	0	5,500	1,500	.....

18	63	F	Carcinoma of fundus of uterus	Hysterectomy and node dissection	Gas, oxygen, ether	1½	0	1+	1,500	500	.....
19	55	F	Carcinoma of fundus of uterus	Hysterectomy and node dissection	Gas, oxygen, ether	2	0	0	500	.....	.....
20	63	F	Carcinoma of fundus of uterus	Hysterectomy and node dissection	Gas, oxygen, ether	2½	2+	0	500	.....	.....
21	40	M	Papilloma of urinary bladder	Cautery removal	Thiopental sodium	1	0	0	.....	.....	.....
22	29	M	Seminoma of testes with metastasis to rt. iliac nodes	Rt. groin and rt. retroperitoneal node dissection; orchiectomy	Gas, oxygen, ether	4½	0	0	1,500	.....	.....
23	54	F	Carcinoma of fundus of uterus with metastasis	Hysterectomy and node dissection; ileostomy	Gas, oxygen, ether, curare	1	1+	0	4,500	.....	.....
24	38	F	Carcinoma of cervix with metastasis	Pelvic exenteration	Gas, oxygen, ether	3	0	0	2,500	500	Jaundice 1st day postoperatively
25	39	F	Carcinoma of cervix	Hysterectomy and node dissection	Gas, oxygen, ether	3	0	1+	4,000	500	.....
26	43	F	Carcinoma of cervix with metastasis	Pelvic exenteration	Gas, oxygen, ether, curare	3	3+	4+	6,000	3,000	Jaundice 3d day postoperatively
27	40	F	Carcinoma of cervix with metastasis to bladder	Hysterectomy; cystectomy	Gas, oxygen, ether	4½	0	2+	3,000	.....	1,500 cc. blood preoperatively
28	44	F	Carcinoma of cervix with metastasis to colon	Resection of cervix and rectosigmoid	Gas, oxygen, ether	1½	0	...	1,500	.....	.....
29	68	F	Metastasis to bladder	Hysterectomy; cystectomy	Gas, oxygen, ether	4½	3+	2+	6,000	.....	Jaundice 2d day postoperatively
30	49	F	Carcinoma of cervix	Hysterectomy and node dissection	Gas, oxygen, ether, curare	2	0	3+	2,500	.....	.....
31	50	M	Carcinoma of colon with stomach metastasis	Subtotal gastrectomy; resection of colon	Gas, oxygen, ether	11	1+	...	3,000	.....	Jaundice 3d day postoperatively 3,000 cc. blood preoperatively
32	48	M	Carcinoma of stomach	Gastrectomy; splenectomy; partial pancreatectomy	Gas, oxygen, ether, curare	2½	0	2+	1,500	1,500	.....
33	68	F	Carcinoma of rectum	Abdominoperineal	Spinal and thiopental sodium	3½	0	0	2,000	.....	Jaundice 1st day postoperatively

* Fall of 20 to 40 mm. for 30 minutes was graded 1+, of 40 to 60 mm. for 30 minutes, 2+, and of 60 to 80 mm. for 15 minutes, 3+. Unobtainable pressure for 15 minutes was graded 4+.

† Temperature elevation above normal and up to 100.5 F. was graded 1+, up to 101.5 F., 2+, up to 103.5 F., 3+, and above 103.5 F., 4+.

‡ Nitrous oxide was the gas used in this combination.

blood during the operation, and all but one (case 17) showed a significant increase in serum bilirubin postoperatively. Of the 7 patients who received 1,000 cc. or less of whole blood, three (cases 10, 14 and 19) had postoperative elevations in serum bilirubin. Seven of the nine

TABLE 2.—*Summary of Results of Liver Function Tests on Thirty-Three Patients Undergoing Abdominal Operations*

	Sulfobromophthalein Retention, %		Bilirubin, Mg./100 Cc.			Thymol Turbidity, Units			Cephalin Flocculation in 48 Hr.		
Case No.	Preoperative	Postoperative*	Preoperative	Postoperative*	Postoperative*	Preoperative	Postoperative*	Postoperative*	Preoperative	Postoperative*	Postoperative*
1	10	30 (1)	0.57	1.98 (1)	0.81 (7)	0.67	1.20 (1)	1.59 (7)	0	3+ (1)	0 (7)
2	2	..	0.86	0.83 (1)	0.57 (7)	0.45	1.20 (1)	1.25 (7)	0	2+ (1)	0 (7)
3	14	29 (6)	0.64	1.46 (2)	0.61 (7)	0.87	0.63 (2)	0.77 (7)	0	0 (2)	0 (6)
4	6	26 (5)	0.31	0.64 (1)	0.47 (7)	1.87	1.53 (1)	3.51 (8)	2+	2+ (1)	3+ (8)
5	2.6	31 (1)	1.24	1.54 (1)	0.68 (7)	1.87	2.02 (1)	0.90 (7)	0	0 (1)	2+ (7)
6	16	31 (1)	0.65	0.57 (1)	0.52 (7)	1.46	1.25 (1)	0.90 (7)	0	1+ (1)	3+ (7)
7	4	28 (1)	1.69	1.16 (1)	0.64 (7)	1.59	0.56 (1)	0.56	0	0 (4)	3+ (6)
8	4	28 (6)	0.22	0.67 (1)	1.05 (6)	1.59	1.3 (1)	1.08 (7)	0	0 (1)	3+ (6)
9	7	10 (2)	0.75	0.62 (2)	0.75 (6)	0.35	2.74 (3)	0.7 (6)	1+	0 (3)	0 (6)
10	3	5 (1)	0.33	0.79 (1)	0.61 (7)	4.79	2.82 (1)	1.33 (7)	0	3+ (1)	2+ (7)
11	4	30 (1)	0.47	0.74 (1)	0.90 (5)	3.51	2.5 (1)	2.0 (5)	3+	3+ (1)	...
12	4	6 (3)	0.43	0.50 (3)	0.50 (4)	1.15	0.56 (3)	0.63 (4)	1+	3+ (3)	2+ (4)
13	32	57 (1)	0.54	2.78 (1) 3.12 (5)	1.22 (14)	2.43	1.73 (1)	0.77 (14)	3+	3+ (1)	3+ (14)
14	3	20 (5)	0.26	0.67 (1)	0.47 (6)	2.6	2.5 (1)	2.6 (5)	2+	2+ (1)	3+ (4)
15	3	..	0.47	0.35 (4)	0.64 (7)	1.33	1.15 (5)	0.45 (7)	1+	3+ (5)	3+ (7)
16	4	22 (4)	0.37	0.54 (2)	0.81 (7)	3.12	2.15 (2)	1.2 (7)	1+	2+ (2)	3+ (7)
17	5	45 (4)	1.74	1.43 (1)	1.56 (5) 1.06 (8)	1.15	1.18 (1)	0.7 (4)	0	0 (1)	...
18	2.6	8 (1)	0.47	1.32 (1)	0.75 (6)	1.0	1.08 (1)	0.4 (6)	2+	2+ (3)	3+ (6)
19	19	35 (1)	0.54	1.26 (2)	0.43 (7)	1.25	1.33 (1)	0.45 (6)	3+	2+ (1)	2+ (6)
20	4	31 (1)	0.54	0.68 (1)	0.47 (6)	1.33	0.56 (1)	0.45 (6)	2+	4+ (1)	...
21	6	32 (1)	0.48	0.4 (1)	....	1.46	0.59 (1)	....	...	...	...
22	5	16 (1)	1.01	1.4 (1)	0.32 (9)	1.80	1.15 (1)	0.96 (6)	2+	3+ (1)	3+ (6)
23	..	..	....	0.6 (4)	2.04 (12)	....	....	....	...	...	...
24	..	..	0.56	4.5 (1)	0.9 (14)	....	1.50 (1)	1.76 (14)	...	0 (1)	...
25	..	..	....	1.3 (1)	2.4 (6)						
26	..	..	....	13.56 (6)	1.02 (30)	....	3.0 (4)	4.6 (6)	...	3+ (4)	3+ (6)
27	..	..	....	4.6 (4)	2.3 (6)	....	1.55 (4)	1.35 (6)	...	3+ (4)	...
28	..	..	0.6	1.8 (1)	....	....	....	....	...	...	...
29	11	..	0.53	0.4 (2)	1.3 (12)	2.6	0.81 (2)	....	4+	...	...
30	..	..	....	2.1 (4)	0.86 (30)	....	....	....	...	...	...
31	..	..	0.34	6.2 (2)	1.98 (30)	....	2.63 (4)	2.85 (30)	...	0 (4)	0 (30)
32	..	..	0.4	5.2 (2)	1.34 (9)	....	....	....	...	...	...
33	..	..	0.61	2.8 (4)	0.91 (14)	....	0.3 (4)	....	...	0 (4)	...

* Numbers in parentheses refer to days after operation.

patients receiving 1,500 cc. of whole blood were observed to have increased serum bilirubin levels. Though there was usually a direct correlation between the amount of blood administered and the level of the serum bilirubin, this was not always true, as evidenced by a fall in serum bilirubin in one patient (case 17) despite the administration of of 5,500 cc. of whole blood.

In six patients (cases 13, 24, 26, 29, 31 and 33) the hyperbilirubinemia was accompanied with clinical jaundice which appeared before the fourth postoperative day. All but one of these six patients (case 13) received at least 2,000 cc. of whole blood, but the amounts ranged from 2,000 to 6,000 cc. There appeared to be no correlation in this group between the amount of blood administered and the appearance and intensity of jaundice.

2. *Sulfobromophthalein Clearance.*—A depression of sulfobromophthalein clearance was observed in 17 patients in group I postoperatively. This occurred usually within the first 24 hours following the operation and was paralleled by corresponding changes in the serum bilirubin level. There were six patients, however, who showed a depression of the sulfobromophthalein clearance and no significant elevation of serum bilirubin. Of these six patients only two (cases 20 and 21) received 500 cc. of blood or less; the remainder were given 1,000 cc. or more of blood.

3. *Thymol Turbidity.*—The upper limit of normal in the determination of thymol turbidity used in this study was a turbidity corresponding to that of 1.75 cc. of a barium sulfate suspension.[4] An elevated thymol turbidity was observed in 13 patients postoperatively. Of these, seven had elevated reactions preoperatively and four had had no preoperative determinations. Two patients (cases 22 and 29) with high preoperative values showed normal results during the postoperative period.

4. *Cephalin Flocculation.*—During the postoperative period abnormal cephalin flocculation was observed in 14 of 22 patients in group I, and of these 14 seven displayed abnormal flocculation about seven days after the operation. Two patients (cases 11 and 13) had abnormal preoperative results which remained the same postoperatively. Two patients (cases 26 and 27) had abnormal postoperative reactions but had had no preoperative determinations.

Six of the 13 patients (cases 5, 9, 24, 26, 27 and 31) with postoperative elevation of thymol turbidity also had abnormal cephalin flocculation. All the patients with abnormal thymol turbidity reactions, except one (case 9), also had elevated serum bilirubin levels postoperatively. All but four (cases 6, 7, 12 and 15) of the 14 patients with abnormal cephalin flocculation postoperatively also had elevated serum bilirubin levels.

5. *Other Reactions.*—Twenty-two patients had no significant fall in blood pressure during the surgical procedures; 14 of these showed significant increases in serum bilirubin postoperatively. Of the five

4. Ley, A. B.; Lewis, J. H., and Davidson, C. S.: Quantitative Determination of Thymol Turbidity Reaction of Serum, J. Lab. & Clin. Med. **31**:910, 1946.

patients with a significant fall in blood pressure during the operation, one (case 20) had a postoperative increase in serum bilirubin. There were five patients with a more serious fall in blood pressure (graded 3+); one of these (case 17) did not have hyperbilirubinemia.

Of the 17 patients in group I with depressed sulfobromophthalein clearances, only two (cases 13 and 15) had significant temperature elevations postoperatively. Fever, therefore, does not appear to explain the abnormal results on liver function tests observed in this group of patients during the postoperative period.

COMMENT

The patients studied here underwent major abdominal operations, in contrast to the patients reported on previously by Tagnon, Robbins and Nichols [2] whose operations were extra-abdominal. In both groups impairment of the sulfobromophthalein clearance was noted during the postoperative period; such impairment was seen more frequently in the series with abdominal operations than in the series previously described.

In addition, and in contrast to the previous studies, a high incidence of postoperative alteration in the cephalin flocculation reaction was observed in the present series of patients. This may have been due to the fact that the type of operations in this group represented a severer injury to the organism than the extra-abdominal operations in the group studied previously.

The data also showed that a high proportion of patients undergoing severe surgical operations with blood transfusions have an elevation of the bilirubin level postoperatively. There was a correlation between postoperative liver impairment, as shown by the results of the tests carried out, and hyperbilirubinemia, but the degree of impairment did not correspond in all cases to the height of the serum bilirubin level. Six patients acquired clinical jaundice. No clear correlation could be discovered between the amount of blood administered and the appearance or the intensity of jaundice. The hyperbilirubinemia and the jaundice were transient and usually subsided in a few days.

A postoperative elevation of the serum bilirubin level may be theoretically due to (*a*) an increased production of bilirubin or (*b*) failure of the bilirubin excretion function of the liver, or both.

There was undoubtedly an increased production of bilirubin when the patients had elevated serum bilirubin levels. It is generally accepted that 30 per cent of the erythrocytes given in a blood transfusion, under conditions such as were present here, are destroyed in the organism within a 24-hour period.[5] In these circumstances approximately 18 Gm.

5. Ross, J. F.; Finch, C. A.; Peacock, W. C., and Sammons, M. E.: In Vitro Preservation and Post-Transfusion Survival of Stored Blood, J. Clin. Investigation **26**:687, 1947.

of hemoglobin is released in the organism following a transfusion of 1 unit (500 cc.) of blood. This would produce approximately 720 mg. of bilirubin, as compared with a normal daily production of approximately 500 mg.[6] Most patients received 3 to 4 units of blood, corresponding to a production of approximately 2,100 to 2,800 mg. of bilirubin in 24 hours. These amounts may well exceed the clearance capacity of even a normal liver. Gilligan and his associates[7] demonstrated that the injection of 5 to 15 Gm. of a stroma-free hemoglobin raised the plasma bilirubin from 0.4 to 1.0 mg. per 100 cc. within six to eight hours. The increased production of bilirubin in these patients may, therefore, constitute an adequate explanation for the high bilirubin level observed during the immediate postoperative period.

On the other hand, the impaired sulfobromophthalein clearance exhibited by these patients immediately after the operation, its persistence for several days and the development of abnormal cephalin flocculation reactions indicate that impairment of the liver was also a factor in the causation of the postoperative hyperbilirubinemia and may explain its persistence beyond the period of increased bilirubin production due to blood transfusion. This opinion is supported by the fact that in dogs sulfobromophthalein clearance parallels bilirubin clearance.[3] If the same applies to man, the patients studied here can be considered as having had postoperative impairment of the bilirubin clearance function of the liver.

The abnormal results on liver function tests observed in this series of patients were not explained by postoperative elevations of the body temperature, since only two of the 17 patients with abnormal sulfobromophthalein clearance had elevated temperatures. Nor does the type of anesthesia seem to have been a determining factor. In 22 of the 33 patients general anesthesia was induced with nitrous oxide, oxygen and ether. Five had spinal anesthesia alone, and five had spinal anesthesia plus thiopental (pentothal®) sodium. Abnormal results on liver function tests were observed in patients of all these groups.

SUMMARY AND CONCLUSIONS

Thirty-three patients undergoing major abdominal operations were studied. Postoperative alteration in results of liver function tests was observed in a high proportion of the patients. The abnormalities were in the sulfobromophthalein clearance in 17 of 22 patients and in the cephalin flocculation in 14 of 22 patients; the changes in thymol turbidity could

6. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 2, Philadelphia, Lea & Febiger, 1949, p. 64.

7. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, J. Clin. Investigation **20**:177, 1941.

not be interpreted in view of the high proportion of preoperative abnormalities.

Twenty-four of the 33 patients had an abnormal serum bilirubin level during the postoperative period, persisting from a few to several days. This was explained by the combination of an increased production of bilirubin associated with blood transfusion and postoperative impairment of liver function.

No satisfactory correlation could be established between the postoperative liver impairment and the character of the operative procedures. However, the operations were of a severe nature, and this may explain the high incidence of liver dysfunction in this series of patients.

The present study confirms and extends previous reports on postoperative dysfunction of the liver. The mechanism of the production of these alterations is not known at present.

The Surgical Services of Memorial Hospital gave permission for study of these patients.

STUDIES ON THE EFFECTS OF PARENTERAL QUINIDINE ADMINISTRATION

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THE NEED for parenteral quinidine therapy has long been recognized. Administration by the intramuscular or intravenous route is indicated in patients requiring this drug who are unable to take the preparation orally because of vomiting, shock or coma and in instances in which rapidity of effect is important.

Following Wenckebach's report [1] in 1914 on the value of quinine in the treatment of cardiac arrhythmias and Frey's subsequent demonstration [2] of the greater effectiveness of its dextroisomer, quinidine, various investigators have attempted to obtain a satisfactory parenteral preparation. In general, these solutions have been unsatisfactory because of their lack of stability. Recently, stable solutions of quinidine have become available.

We have studied the effects of quinidine lactate administered parenterally on 59 subjects divided into three groups. Group A consisted of 22 persons with normal hearts, group B of 15 with abnormal hearts (with regular sinus rhythm) and group C of 22 with cardiac arrhythmias. By means of changes in the Q-T interval in serial electrocardiograms, the earliest and maximal effect and the total duration of quinidine effect were determined. We also observed variations in the P-R interval and QRS complex. Special note was made of all manifestations of clinical toxicity accompanying the parenteral use of quinidine lactate.

Quinidine lactate was supplied by Eli Lilly & Company, Indianapolis 6.

From the service of Julius Burstein, M.D., Department of Electrocardiography, Morrisania City Hospital.

1. Wenckebach, K. E.: Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipzig, W. Engelmann, 1914.

2. Frey, W.: Weitere Erfahrungen mit Chinidin bei absoluter Herzunregelmässigkeit, Klin. Wchnschr. **55**:849-853, 1918.

METHOD

Quinidine lactate was administered parenterally (intramuscularly or intravenously) to three groups of subjects.

Group A consisted of 22 subjects with normal hearts as determined by cardiac survey. These were hospital patients who ranged in age from 20 to 53 years. After control electrocardiograms and blood pressure readings were taken, 15 subjects were given 0.65 Gm. of quinidine lactate intramuscularly and seven subjects were given 0.65 Gm. intravenously over an interval of one to five minutes. In those given the drug intramuscularly, electrocardiograms were taken at 2, 5, 15, 30, 60, 90 and 120 minutes and at 4, 6, 9, 12, 24, 27, 30, 33 and 36 hours following administration. In no subject were recordings made at each of these times. There were nine observations at two minutes; five at 5, 15, 30, 60 and 90 minutes; 15 at 120 minutes; nine at four hours; 10 at 6, 9, 12, 27, 30, 33 and 36 hours. There were 13 observations at 24 hours. Blood pressures were again observed at two hours. In those who received the drug intravenously, electrocardiograms were taken at 5, 15, 30, 60, 90 and 120 minutes and at 24 hours. There were seven observations at 5, 15, 30, 60 and 120 minutes; six at 90 minutes, and four at 24 hours. Blood pressures were observed at the same time intervals for two hours.

Group B consisted of 15 subjects with heart disease. Three had arteriosclerotic heart disease; two had hypertensive and arteriosclerotic heart disease; seven had arteriosclerotic heart disease with recent myocardial infarction (2½ to 4 weeks previously); two had rheumatic heart disease, one showing activity; one had Wolff-Parkinson-White syndrome. As with group A, after control electrocardiograms and blood pressure readings were taken, all subjects were given 0.65 Gm. of quinidine lactate intramuscularly (except for a 12 year old boy [case 31], who received 0.40 Gm. of quinidine). Electrocardiograms were taken at intervals similar to those for group A. There were 11 observations at two minutes, five at five minutes, three at 15 minutes, five at 30 minutes, nine at 60 minutes, five at 90 minutes, 12 at 120 minutes, four at three hours and eight at 4, 6, 9 and 12 hours. Four observations were made at five hours, 13 at 24 hours, eight at 27 hours, six at 30 hours and eight at 33 and 36 hours. Blood pressures were again observed at two hours.

The Q-T interval was measured to 0.01 second and corrected for rate, using Taran and Szilagyi's modification[3] of Bazett's formula; the QT_c refers to this corrected Q-T measurement. The increase in QT_c in seconds above the control value was averaged for each time interval in the above groups and charted (tables 1 and 2). Only changes in QT_c of 0.01 second or longer were considered as significant. Changes in P-R and QRS intervals were also noted.

Group C consisted of 22 subjects with cardiac arrhythmias, with normal and abnormal hearts. There were eight persons with supraventricular tachycardia, three with auricular flutter, six with auricular fibrillation, three with ventricular tachycardia and two with Wolff-Parkinson-White syndrome. Seven of these subjects received quinidine intravenously; the rest received the drug intramuscularly. In many of the subjects multiple doses were administered. The individual doses ranged from 0.40 to 1.3 Gm.; the total doses ranged from 0.40 to 4.15 Gm. Electrocardiograms were taken at frequent intervals; esophageal leads were taken in several subjects to determine the type of arrhythmia (table 3).

3. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, Am. Heart J. **33**:14-26, 1947.

All subjects were supine at the time electrocardiograms were taken; otherwise no change in ward routine was made. A test dose of quinidine was not used. No drug known to have an effect on the Q-T interval had been given previously (except in cases 19 and 27, in which 2.0 mg. of lanatoside C [cedilanid®] had been given 12 and 18 hours, respectively, prior to the administration of quinidine). Each subject was carefully observed for manifestations of clinical toxicity.

RESULTS

A single dose of 0.65 Gm. of quinidine lactate was administered parenterally to 37 subjects with regular sinus rhythm. Fifteen with known cardiac disease and 15 with normal hearts received the drug intramuscularly; seven with normal hearts were given the drug intra-

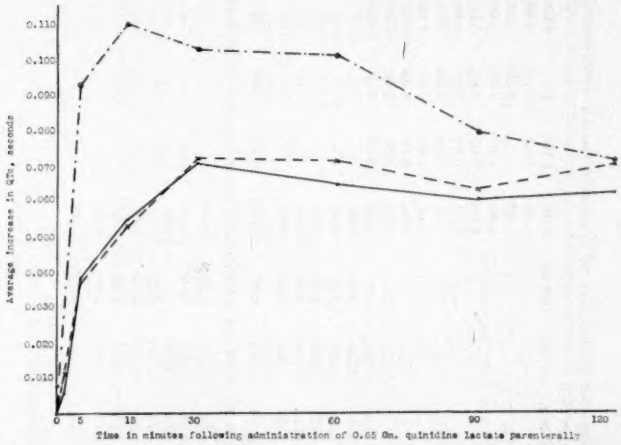

Fig. 1.—Onset of effect and attainment of maximal effect following intravenous and intramuscular administration of quinidine, as estimated by changes in QT_c. Solid line indicates values for subjects with normal hearts given quinidine intramuscularly; broken line, values for subjects with abnormal hearts given quinidine intramuscularly, and line of dots and dashes, values for subjects with normal hearts given the drug intravenously.

venously. The changes in QT_c were observed at various times following injection; these were averaged and charted (figs. 1 and 2). All subsequent statements regarding changes in QT_c refer to the average of the deviations from the control value observed at each time interval. It should be noted that pronounced variations occurred in the response of some persons.

Response of Normal Persons to 0.65 Gm. of Quinidine Lactate Given Intravenously.—Five minutes after the start of the injection the QT_c had increased to 85 per cent of the maximum level, and a peak effect was

TABLE 1.—*QT_c Following Administration of 0.65 Gm. of Quinidine Lactate Intramuscularly in Normal Persons*

Case No.	Control	2 Min.	5 Min.	15 Min.	30 Min.	60 Min.	90 Min.	2 Hr.	4 Hr.	6 Hr.	9 Hr.	12 Hr.	24 Hr.	27 Hr.	30 Hr.	33 Hr.	36 Hr.
1	0.371	0.380	.....	.....	.....	.....	.....	0.530	0.530	0.433	0.398	0.408	0.405	0.378	0.396	0.378	0.369
2	0.375	.....	.....	.....	.....	.....	.....	0.477	.....	0.414	0.427	0.404	0.402	0.372	0.396	0.397	0.394
3	0.382	0.371	.....	.....	.....	.....	.....	0.393	0.419	0.427	0.405	0.428	0.400	0.379	0.402	0.369	0.385
4	0.387	0.383	.....	.....	.....	.....	.....	0.438	0.448	0.431	0.417	0.399	0.389	0.376	0.385	0.384	0.381
5	0.383	0.381	.....	.....	.....	.....	.....	0.454	0.419	0.409	0.420	0.405	0.390	0.391	0.394	0.390	0.387
6	0.378	0.380	.....	.....	.....	.....	.....	0.408	0.426	0.414	0.378	0.383	0.379	0.369	0.372	0.383	0.373
7	0.404	0.416	.....	.....	.....	.....	.....	0.480	0.486	0.427	0.446	0.407	0.410	0.397	0.388	0.409	0.408
8	0.408	0.414	.....	.....	.....	.....	.....	0.434	0.430	0.409	0.412	0.411	0.403	0.396	0.387	0.399	0.402
9	0.364	0.402	.....	.....	.....	.....	.....	0.443	0.425	0.421	0.410	0.408	0.401	0.380	0.388	0.391	0.376
10	0.387	0.394	.....	.....	.....	.....	.....	0.404	0.406	0.387	0.402	0.372	0.379	0.352	0.368	0.365	0.376
11	0.377	.....	0.409	0.435	0.427	0.432	0.433	0.445	.....	.....	.....	.....	.....	.....	.....	.....	.....
12	0.393	.....	0.411	0.424	0.424	0.424	0.414	0.408	.....	.....	.....	.....	.....	.....	.....	.....	.....
13	0.407	.....	0.485	0.528	0.561	0.530	0.521	0.506	.....	.....	.....	.....	0.422	.....	.....	.....	.....
14	0.360	.....	0.369	0.373	0.411	0.402	0.402	0.417	.....	.....	.....	.....	0.366	.....	.....	.....	.....
15	0.378	.....	0.439	0.436	0.456	0.457	0.453	0.452	.....	.....	.....	.....	0.402	.....	.....	.....	.....
Average increase in QTc	.....	0.006	0.038	0.054	0.071	0.064	0.060	0.062	0.058	0.033	0.028	0.019	0.013	0.002	0.004	0.002	0.001
QTc Following Administration of 0.65 Gm. of Quinidine Lactate Intravenously in Normal Persons																	
16	0.403	.....	0.538	0.498	0.496	0.516	0.499	0.490	.....	.....	.....	.....	0.422	.....	.....	.....	.....
17	0.379	.....	0.520	0.604	0.595	0.595	0.550	0.517	.....	.....	.....	.....	0.422	.....	.....	.....	.....
18	0.392	.....	0.475	0.508	0.477	0.542	.....	0.485	.....	.....	.....	.....	0.409	.....	.....	.....	.....
19 *	0.368	.....	0.490	0.480	0.495	0.465	0.448	0.446	.....	.....	.....	.....	0.450	.....	.....	.....	.....
20	0.351	.....	0.458	0.414	0.424	0.417	0.400	0.405	.....	.....	.....	.....	.....	.....	.....	.....	.....
21	0.431	.....	0.504	0.505	0.497	0.527	0.443	0.455	.....	.....	.....	.....	.....	.....	.....	.....	.....
22	0.415	.....	0.506	0.488	0.479	0.473	0.480	0.441	.....	.....	.....	.....	.....	.....	.....	.....	.....
Average increase in QTc	.....	.....	0.093	0.110	0.103	0.101	0.079	0.071	.....	.....	.....	.....	0.040	.....	.....	.....	.....

* Twelve hours following administration of 2.0 mg. of lanatoside C (cedilanid †) intravenously.
† Registered trademark.

TABLE 2.—*QT_c Following Administration of 0.65 Gm. of Quinidine Lactate Intramuscularly in Abnormal Persons*

Case No.	Control	2 Min.	5 Min.	15 Min.	30 Min.	60 Min.	90 Min.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	9 Hr.	12 Hr.	24 Hr.	27 Hr.	30 Hr.	33 Hr.	36 Hr.
23*.....	0.402	.....	0.435	0.481	0.492—	0.480	0.492	0.492	.....	.....	.....	.....	.....	.....	0.429	.....	.....	.....	.....
24.....	0.399	0.405	0.440	.....	0.478	0.470	0.461	0.468	.....	.....	.....	.....	.....	.....	0.380	.....	.....	.....	.....
25.....	0.427	.....	0.480	0.480	0.530	0.485	0.485	0.487	.....	.....	.....	.....	.....	.....	0.478	.....	.....	.....	.....
26.....	0.378	.....	0.406	0.406	0.406	[illegible]	0.424	0.433	.....	.....	.....	.....	.....	.....	0.424	.....	.....	.....	.....
27.....	0.413	0.446	0.442	.....	0.4[illegible]	0.475	0.471	.....	.....	.....	.....	.....	.....	.....	0.392	.....	.....	.....	.....
28.....	0.460	0.417	.....	.....	.....	.....	.....	0.466	.....	0.467	.....	0.458	0.431	0.417	0.442	0.412	0.437	0.405	0.410
29.....	0.464	0.477	.....	.....	.....	.....	.....	0.506	.....	0.485	.....	0.487	0.496	0.482	0.468	0.443	0.436	0.462	0.468
30.....	0.385	0.438	.....	.....	.....	.....	.....	0.540	.....	0.504	.....	0.494	0.436	0.450	0.410	0.410	0.395	0.407	0.375
31†.....	0.442	0.428	.....	.....	.....	.....	.....	0.480	.....	0.486	.....	0.486	0.445	0.438	0.441	0.424	0.438	0.438	0.432
32.....	0.560	0.555	.....	.....	.....	0.615	.....	0.615	0.615	0.615	0.606	0.614	0.583	.....	.....	.....	.....	.....	.....
33.....	0.428	0.444	.....	.....	.....	0.496	.....	0.445	0.436	0.441	0.424	0.477	0.433	0.402	0.408	0.410	.....	0.402	0.413
34.....	0.397	0.414	.....	.....	.....	0.509	.....	0.530	0.526	0.576	0.576	0.539	0.534	0.529	0.408	0.438	.....	0.417	0.408
35.....	0.379	0.373	.....	.....	.....	0.430	.....	0.443	0.450	0.450	0.440	0.410	0.377	0.373	0.373	0.355	0.353	0.351	0.357
36.....	0.445	0.442	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.445	0.430	0.482	0.420	0.468	0.447	0.450
Average increase in QTc.....	0.011	0.037	0.053	0.072	0.068	0.063	0.070	0.066	0.071	0.071	0.064	0.081	0.023	0.015	0.004	0.002	0.001	0.003	

* Eighteen hours following administration of 2.0 mg. of lanatoside C (cedilanid ‡) intravenously.
† A 12 year old boy given 0.40 Gm. of quinidine lactate intramuscularly.
‡ Registered trademark.

TABLE 3.—*Response of Patients with Cardiac Arrhythmias to Quinidine Administration*

Case Number	Type of Arrhythmia	Control Rate	Dose of Quinidine Lactate, Gm.	Time of Initial Effect *	Time of Maximal Effect *	Minimum Duration of Maximal Effect *	Rate at Time of Maximal Effect	Comment
38	Supraventricular tachycardia	A. R.† 200	0.65 I. M.	None	.....	.....	.....	2d dose after 2 hr.
			0.65 I. M.	2 min.	2 min.	.....	Reversion to R. S. R.‡	Vomiting 2 to 3 hr. after 2d dose
39	Supraventricular tachycardia	A. R. 204	0.65 I. V.	15 min.	60 min.	.....	Reversion to R. S. R.	Vomiting 45 min. after injection
40	Supraventricular tachycardia	A. R. 180	0.65 I. M.	2 hr.	2 hr.	.....	Reversion to R. S. R.	No change in rate until reversion
41	Supraventricular tachycardia	A. R. 182	0.65 I. M.	1 hr.	1 hr.	.....	Reversion to R. S. R.	Tachycardia with varying A-V block
42	Supraventricular tachycardia	A. R. 180	0.65 I. M.	30 min.	30 min.	.....	Reversion to R. S. R.	Subsequent episode reverted to R. S. R. in 40 min. following 0.65 Gm. of quinidine orally
43	Supraventricular tachycardia	A. R. 180	0.65 I. M.	15 min.	45 min.	4 hr.	165	QRS widened from 0.11 to 0.13 sec.; 2d dose after 4 hr.
		165	0.65 I. M.	15 min.	70 min.	2 hr.	152	3d dose after 2 hr. QRS to 0.14 sec.
		152	0.65 I. M.	35 min.	80 min.	2 hr.	142	QRS to 0.16 sec.
44	Supraventricular tachycardia	A. R. 200	0.65 I. M.	5 min.	60 min.	3 hr.	180	2d dose after 3 hr.
		180	0.65 I. M.	15 min.	15 min.	30 min.	169	3d dose after 2½ hr.
		169	0.65 I. M.	None	.....	.....	167	4th dose I. V., 14 hr. later
		171	0.40 I. V.	3 min.	3 min.	.....	Reversion to R. S. R.	Vomiting immediately after injection
45	Supraventricular tachycardia	A. R. 182	0.65 I. M.	None	.....	.....	.....	Varying A-V block; transient BBB appeared 45 min. after 1st dose; 2d dose after 2 hr.
			0.65 I. M.	2 min.	2 min.	.....	Reversion to R. S. R.	Back to auricular tachycardia with BBB in 15 min.; R. S. R. in 1½ hr.
46	Auricular flutter	A. R. 200	0.65 I. M.	15 min.	30 min.	2 hr.	222	2d dose after 2 hr.
		222	0.65 I. M.	15 min.	30 min.	2 hr.	204	3d dose after 2 hr.
		204	0.65 I. M.	30 min.	30 min.	2 hr.	190	Vomiting 30 min. after 3d dose; A.R. 226 17½ hr. after 3d dose
47	Auricular flutter	A. R. 286	0.65 I. V.	2 min.	5 min.	5 min.	194	At 12 min. 1:1 response resembling ventricular tachycardia
48	Auricular flutter	A. R. 286	0.65 I. M.	5 min.	30 min.	8¼ hr.	240	Widening of QRS
		273	0.65 I. V.	2 min.	4 min.	30 min.	176	Shocklike picture as injection was completed; at 4 min. 1:1 response and widening of QRS, resembling ventricular tachycardia; at 1 hr. A.R. was 214

49.....	Auricular fibrillation	V. R. 140	0.65 I. M.	6 min.	6 min.	.....	Reversion to R. S. R.	
50.....	Auricular fibrillation	V. R. 150	0.65 I. M.	30 min.	30 min.	.....	Reversion to R. S. R.	Frequent VPC's eliminated by quinidine
51.....	Auricular fibrillation	A. R. 407	0.65 I. M.	1 hr.	1 hr.	4 hr.	375	2d dose after 4 hr.
		375	0.65 I. M.	1 hr.	1 hr.	2 hr.	329	3d dose after 2 hr.
		329	0.65 I. M.	1 hr.	2 hr.	.....	Reversion to R. S. R.	Reverted to auricular fibrillation between 36 and 60 hr. after last dose
52.....	Auricular fibrillation	V. R. 185	0.65 I. M.	.....	.....	.....	.....	V.R. at 2 hr. decreased to 165; QRS widened from 0.11 to 0.14 sec. at 1 hr.
53.....	Auricular fibrillation	V. R. 150	0.65 I. M.	.....	.....	.....	.....	Reversion to R.S.R. between 2 and 7 hr.
54.....	Auricular fibrillation	V. R. 120	0.65 I. M	40 min.	40 min.	.....	Reversion to R. S. R.	
55.....	Wolff-Parkinson-White syndrome	Predominantly typical of syndrome	0.65 I. M.	2 min.	5 min.	3 hr.	Reversion to R. S. R.	Paroxysmal Wolff-Parkinson-White syndrome
56.....	Wolff-Parkinson-White syndrome	.....	0.65 I. M.	90 min.	90 min.	2½ hr.	Reversion to R. S. R.	Back to Wolff-Parkinson-White syndrome at 3½ hr.
			0.65 I. V.	During injection	During injection	5 hr.	Reversion to R. S. R.	Back to Wolff-Parkinson-White syndrome at 6 hr.
								Quinidine given orally gave R.S.R. in 90 min. lasting at least 3 hr.
57.....	Ventricular tachycardia	V. R. 231	0.65 I. M.	60 min.	2 hr.	2 hr.	94	
58.....	Ventricular tachycardia	V. R. 180	0.65 I. V.	.....	.....	.....	.....	2d dose 3 hr. after 1st, effect occurred 4 hr. later
			0.65 I. M	.....	7 hr.	.....	136	
59.....	Ventricular tachycardia	V. R. 182	0.65 I. M.	70 min.	70 min.	2 hr.	171	2d dose after 2 hr.
		171	0.65 I. M.	15 min.	60 min.	2 hr.	150	3d dose after 2 hr.
		150	0.65 I. M.	30 min.	60 min.	2 hr.	136	4th dose after 2 hr.
		136	1.0 I. M.	30 min.	60 min.	2 hr.	125	5th dose after 2 hr.
		125	1.30 I. M.	30 min.	60 min.	.....	Reversion to nodal rhythm	

* Time following parenteral administration of quinidine.
† A.R. indicates auricular rate, and V.R., ventricular rate.
‡ R.S.R. indicates regular sinus rhythm.

noted within 15 minutes. The magnitude of the peak effect was about 50 per cent greater than that observed with an identical dose of quinidine given intramuscularly. The maximal response was maintained for at least 60 minutes. Ninety minutes after administration the effect had decreased to 70 per cent. At 24 hours 35 per cent of peak effect persisted.

Toxic reactions occurred in every subject; in one (case 17) alarming symptoms of collapse appeared. Within 15 minutes after the injection, this subject experienced flushing, dizziness and palpitations; the blood pressure fell from 115/80 to 85/60, and the patient appeared to be in shock. This reaction persisted for about 15 minutes and then subsided. Flushing occurred in four subjects, dizziness in two, palpitations in two and vomiting in one.

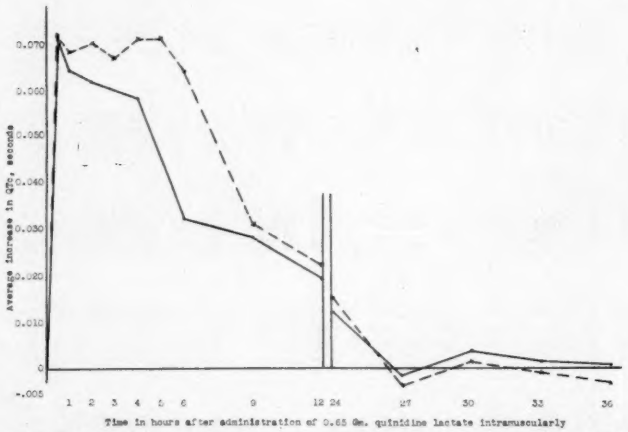

Fig. 2.—Duration of maximal effect and total duration of effect following quinidine given intramuscularly, as estimated by changes in QT_c. Solid line indicates values for subjects with normal hearts and broken line values for subjects with abnormal hearts.

Response of Normal Persons to 0.65 Gm. of Quinidine Lactate Given Intramuscularly.—Two minutes after the injection there was no significant average change in the QT_c, although about 20 per cent of the subjects showed a definite prolongation. At five minutes there was a decided increase in QT_c, which represented approximately 50 per cent of peak effect. By 15 minutes about 70 per cent of the maximal effect had been attained, and at 30 minutes the increase had reached its highest level.

This maximal effect was maintained for at least two hours and then began to decrease, so that four hours after the injection there was

approximately 85 per cent of peak effect, at six hours 50 per cent, at nine hours about 40 per cent and at 12 hours 30 per cent. There was still a definite effect noted at 24 hours—approximately 20 per cent of the maximum effect. From 27 to 36 hours the QT_c showed no significant difference from the control values, although one patient displayed persistence of effect for at least 36 hours.

No significant change was noted in P-R interval or QRS duration in these subjects, except for a slight increase in width of the QRS complex (0.12 to 0.14 second) in one (case 7). There were no constant changes noted in blood pressure readings taken two hours following administration. No evidence of clinical toxicity was noted, except in a patient (case 9) who had nausea, sweating, dizziness and pallor 30 minutes after the injection; these effects lasted 15 to 30 minutes.

Response of Subjects with Abnormal Hearts to 0.65 Gm. of Quinidine Lactate Given Intramuscularly.—In this group there was a slight but significant average rise in QT_c within two minutes, although not all subjects showed an increase. At five minutes there was a definite prolongation, approximating 50 per cent of peak effect, and at 15 minutes 70 per cent of maximal effect had been attained. The greatest increase in QT_c was noted at 30 minutes, and the magnitude of this prolongation was almost identical with that observed in the normal group.

The maximal response was maintained for at least six hours and then decreased sharply, so that at nine hours there was approximately 45 per cent and at 12 hours 23 per cent of peak effect. At 24 hours a slight but definite effect persisted, while from 27 to 36 hours no effect was evident.

No significant changes in P-R or QRS duration were observed. Two subjects showed a decrease in blood pressure readings taken two hours after injection from 120/90 to 110/70, case 34, and from 100/75 to 70/50, case 37. One patient with bundle branch block (case 37) showed definite widening of the QRS complex (0.14 to 0.16 second) at the time of maximal quinidine effect. The only sign of clinical toxicity noted was the occurrence of nausea in two subjects (cases 33 and 34) about three hours after administration. The injections were painless in all subjects.

Response of Subjects with Cardiac Arrhythmias.—The effects of single and multiple parenteral doses of quinidine were studied in 22 subjects with cardiac arrhythmias. We were not interested primarily in treating the disturbances of rhythm but rather in observing the onset, magnitude and duration of effect as gaged by auricular or ventricular rates (table 3).

Supraventricular Tachycardia (Cases 38 to 45): In three patients (cases 40, 41 and 42) there was reversion to regular sinus rhythm occurring from 30 minutes to two hours after a single intramuscular dose of 0.65 Gm. of quinidine. No change in rate was noted prior to reversion.

In one subject (case 39) 0.65 Gm. of quinidine lactate administered intravenously caused reversion to regular sinus rhythm within 60 minutes.

In two patients (cases 38 and 45) no effect was observed on auricular rate with a single dose of 0.65 Gm. of quinidine intramuscularly; two minutes following a second dose, given at the end of two hours, there was reversion to regular sinus rhythm. In one patient (case 45) the control tracing showed auricular tachycardia with varying auriculoventricular block. Forty-five minutes after the first dose of quinidine, paroxysms of intraventricular block appeared, with no change in auricular rate. At two hours, a second dose was administered, and two minutes later there was regular sinus tachycardia at a rate of 120 per minute. Fifteen minutes later the rhythm was again auricular tachycardia at the control rate, with intraventricular block and a Wenckebach type of auriculoventricular block. Ninety minutes after the second dose the tracing showed regular sinus rhythm, with normal QRS complexes.

In two subjects quinidine given intramuscularly was ineffective in restoring regular sinus rhythm. In one (case 43) three doses of 0.65 Gm. of quinidine were administered intramuscularly over a period of eight hours; the auricular rate slowed successively with each dose. The maximal effect occurred about one hour after each dose and was maintained for periods of four, two and two hours until subsequent doses were given. In the other (case 44) three doses of 0.65 Gm. of quinidine, administered intramuscularly at two hour intervals, caused slowing of the rate after the first and second doses but no further slowing after the third. Quinidine, 0.40 Gm., was administered intravenously 14 hours after the third intramuscular dose, and the rhythm reverted to normal within three minutes.

Auricular Flutter (cases 46 to 48): In two subjects (cases 47 and 48) a single dose of 0.65 Gm. of quinidine was administered intravenously. In one of these (case 47)[4] slowing of auricular rate was apparent within two minutes of the start of the injection. Maximal slowing occurred within five minutes. Twelve minutes after administration a 1:1 auriculoventricular response with intraventricular block, resembling ventricular tachycardia, was noted. Within 15 minutes the auricular rate had begun to increase and at 24 hours had returned to the control level.

In the second subject (case 48) 0.65 Gm. of quinidine lactate was administered intravenously over a period of five minutes; a maximal effect on auricular rate was produced before the injection was completed. Concomitant with the marked slowing of auricular rate there occurred

4. Blinder, H.; Burstein, J.; Horowitz, W., and Gersh, E.: Intravenous Quinidine Therapy for Auricular Flutter Resulting in 1:1 Auricular Flutter and Other Changes, New York State J. Med. **50**:298-299, 1950.

an intermittent 1 : 1 response of the ventricles, with an associated increase in the width of the QRS complex, simulating ventricular tachycardia. At the end of two hours the effect on auricular rate persisted but was only about 50 per cent of the maximal effect.

An identical dose of quinidine given intramuscularly to this subject produced a slowing of auricular rate which began within five minutes of administration and reached a maximum within 30 minutes. The magnitude of the peak effect was about half that observed with intravenous administration of quinidine. The maximal effect was maintained for at least 8½ hours.

To one patient (case 46) three doses of 0.65 Gm. of quinidine were administered intramuscularly at two hour intervals. After each dose, a slowing of auricular rate was noted within 15 minutes. A peak effect was reached within 30 minutes, which was maintained for at least two hours, until the subsequent dose was administered. Reversion to regular sinus rhythm occurred 72 hours after the last dose of quinidine.

Auricular Fibrillation (cases 49 to 54): In three subjects (cases 49, 50 and 54) a single dose of 0.65 Gm. of quinidine given intramuscularly caused reversion to regular sinus rhythm in six to 40 minutes.

In another subject (case 51) no slowing of auricular rate occurred within 15 minutes of an intramuscular dose of 0.65 Gm. of quinidine. Maximal slowing was noted at one hour, which persisted for four hours, when a second dose of 0.65 Gm. was administered intramuscularly. This was followed by a further decrease in auricular rate, which was maximal at one hour and persisted until two hours after injection, when a third dose was given. Further slowing of auricular rate was noted at the end of an hour, and within two hours regular sinus rhythm had been restored.

In the fifth subject (case 53) auricular rate could not be determined. Slight slowing of ventricular rate occurred within two hours following administration of 0.65 Gm. of quinidine intramuscularly; regular sinus rhythm returned between two and seven hours.

In another patient (case 52) whose auricular rate could not be measured, slight slowing of ventricular rate occurred within two hours of the administration of 0.65 Gm. of quinidine intramuscularly. The width of the QRS complex increased from 0.11 to 0.14 second at one hour following injection. There was no reversion in this subject.

Wolff-Parkinson-White Syndrome (cases 55 and 56): In the first subject (case 56) 0.65 Gm. of quinidine lactate administered intravenously caused reversion to normal conduction during the injection, which lasted five minutes. Between three and five hours after the injection the Wolff-Parkinson-White pattern was resumed. An identical intramuscular dose of quinidine in this subject produced a normal pattern

within 90 minutes, which persisted for 2½ to 3½ hours; the same dose of quinidine sulfate orally caused reversion to normal within 90 minutes, lasting at least three hours.

The other subject (case 55) had paroxysmal Wolff-Parkinson-White syndrome, with most of the complexes showing the abnormal form. Within five minutes of the injection of 0.65 Gm. quinidine intramuscularly, all the complexes were of the normal variety, and at least three hours elapsed before abnormal complexes reappeared.

Ventricular Tachycardia (cases 57 to 59): In one subject (case 59) quinidine was administered intramuscularly at two hour intervals for five doses. The first three doses were 0.65 Gm., the fourth 1.0 Gm. and the fifth 1.3 Gm. The ventricular rate decreased progressively with each dose. Onset of effect occurred within 15 minutes to one hour after the injection; maximal effect was attained within one hour and persisted for at least two hours until the next dose. One hour after the fifth dose the ventricular tachycardia was abolished and replaced by nodal tachycardia.

In the second patient (case 58) 0.65 Gm. of quinidine was administered intravenously, followed three hours later by the same dose given intramuscularly. Four hours after the second dose slowing of ventricular rate was observed.

A subject (case 57) with chronic fibrillation had paroxysms of ventricular tachycardia. After administration of 0.65 Gm. of quinidine intramuscularly, the ventricular rate during the paroxysms began to decrease within one hour, and in two hours the rate was less than half the control value.

COMMENT

During the initial phases of this investigation it became apparent that the intravenous administration of 0.65 Gm. of quinidine lactate is a hazardous procedure; after limited trial (12 cases), its use was discontinued. When injected in several minutes' time, quinidine produced toxic reactions in every instance, while in three cases there occurred alarming symptoms of syncope or collapse, which were probably due to a sudden decrease in peripheral resistance [5] and precipitous fall in blood pressure.[6] The intravenous use of quinidine in patients with auricular flutter or fibrillation bears the additional danger of producing a sudden increase in ventricular rate because of the decided slowing of the auricular pacemaker and the concomitant increase in auriculoventricular conduction, as occurred in cases 47 and 48. Moreover, the exposure of a damaged

5. Ferrer, M. I.; Harvey, R. M.; Werkö, L.; Dresdale, D. T.; Cournand, A., and Richards, D. W., Jr.: Some Effects of Quinidine Sulfate on the Heart and Circulation in Man, Am. Heart J. **36**:816-837, 1948.

6. Ferrer and others.[5] Weisman, S. A.: Quinidine, "Pure Quinidine" and Hydroquinidine: I. Toxicity, Am. Heart J. **24**:545-549, 1942.

heart to sudden high concentrations of quinidine might more readily cause standstill of the sinus or other pacemakers than has occurred with oral administration of the drug.[7]

Wilson and Wishart[8] in 1926 reported a fatality following the use of quinidine intravenously and concluded that the toxic effects of this route of administration made its therapeutic use impractical. Schwartz and Jezer[9] reported the occurrence of ventricular fibrillation in susceptible persons following the intravenous administration of ¼ to 1½ grains (15 to 75 mg.) of quinidine dihydrochloride. Strong and Munroe[10] described the occurrence of epileptiform seizures and loss of consciousness in a patient given quinidine sulfate intravenously.

Ambrust and Levine[11] treated 31 patients with ventricular tachycardia by the administration of quinidine hydrochloride intravenously and reported four fatalities due to quinidine toxicity. In three of the fatal cases 0.1 to 0.6 Gm. of quinidine was administered in several minutes. In the fourth case death followed the administration of 0.6 Gm. of quinidine injected in 20 minutes. It is apparent from the published experiences of others, as well as our own, that the toxicity of quinidine given intravenously is directly related to the speed of injection. The above authors[11] suggested that 0.6 Gm. of quinidine be administered by intravenous drip over a period of one hour. This method, while less hazardous, seems to offer little advantage over the intramuscular route because of the time required.

When given intramuscularly, quinidine lactate is relatively painless and no more toxic than quinidine administered orally in similar dosage, the incidence of nausea, headache, tinnitus, etc., being almost equal by both routes. The intramuscular route has the added advantages of providing more rapid and uniform absorption and of obviating possible gastric intolerance to the drug. We found no consistent changes in blood pressure and pulse rate concurrent with the time of maximum cardiac effect.

The effects of a single intramuscular dose of 0.65 Gm. of quinidine lactate, as determined by changes in the corrected Q-T interval (QT_c), were observed in subjects with normal hearts. Fifty per cent of maximal

7. Wolff, L., and White, P. D.: Auricular Standstill During Quinidine Sulfate Therapy, Heart **14**:295-303, 1929.

8. Wilson, F. N., and Wishart, S. W.: The Effects Produced by Intravenous Injection of Quinidine and Other Drugs upon the Mechanism of the Heart Beat, Tr. A. Am. Physicians **41**:55-66, 1926.

9. Schwartz, S. P., and Jezer, A.: Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, Am. Heart J. **9**:792-801, 1934.

10. Strong, G. F., and Munroe, D. S.: Paroxysmal Ventricular Tachycardia, with Report of an Unusual Case, Am. Heart J. **19**:486-491, 1940.

11. Ambrust, C. A., Jr., and Levine, S. A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases, Circulation **1**:28-40, 1950.

cardiac effect was attained within five minutes; by 15 minutes 70 per cent of peak effect was noted, and within 30 minutes the response had become maximal. The times of onset of effect and attainment of maximal response were almost identical in subjects with abnormal hearts; however, the duration of peak effect was between two and four hours in those with normal hearts as compared with at least six hours in subjects with abnormal hearts. In both groups a small but definite quinidine effect persisted for 24 hours.

After the intravenous administration of an identical dose of quinidine lactate in subjects with normal hearts, 85 per cent of peak effect was attained within five minutes. A maximal effect 50 per cent greater in magnitude than that obtained by intramuscular administration was reached in 15 minutes and maintained for one hour. At two hours there was a fall to 65 per cent of maximal effect; beyond this time the only observations made in the intravenous studies were 24 hour tracings which showed the persistence of a significant quinidine effect.

It should be noted that the effects described above are average and that there were wide variations in individual cases (tables 1 and 2).

According to Sagall and his associates,[12] a maximal response is obtained in about 1¾ hours following the oral administration of 0.6 Gm. of quinidine sulfate and is maintained about four hours. Thus, the comparative times of attainment of maximal response are 15 minutes with intravenous, 30 minutes with intramuscular and 1¾ hours with oral administration. The duration of maximal effect is about equal following oral and intramuscular use of quinidine.

There has not been complete agreement regarding the correlation between plasma levels of quinidine and its cardiac action.[13] From the limited information available at present, maximal blood levels of quinidine following the intramuscular administration of 0.6 Gm. of quinidine lactate are reached in one to three hours and fall to 25 to 50 per cent of peak levels within four hours.[14] Our findings of the earlier attain-

12. Sagall, E. L.; Horn, C. D., and Riseman, J. E. F.: Studies on the Action of Quinidine in Man: I. Measurement of Speed and Duration of Effect Following Oral and Intramuscular Administration, Arch. Int. Med. **71**:460-473 (April) 1943.

13. (*a*) Linenthal, A. J., and Freedberg, A. S.: Medical Progress: Measures Used in the Prevention and Treatment of Cardiac Arrhythmias, New England J. Med. **241**:570-578; 616-620, 1949. (*b*) Wégria, R., and Boyle, M. N.: Correlation Between Effect of Quinidine Sulfate on Heart and Its Concentration in Blood Plasma, Am. J. Med. **4**:373-382, 1948. (*c*) Wégria, R.: Correlation Between Effect of Quinidine Sulfate on Rate of Circus Movement in Auricular Fibrillation and Its Concentration in Blood Plasma, J. Clin. Investigation **26**:1200, 1947.

14. Kalmensohn, R. W., and Sampson, J. J.: Studies of Plasma Quinidine Content in Relation to Single Dose Administration, Toxic Manifestations and Therapeutic Effect, Am. J. Med. **6**:393-394, 1949.

ment and longer duration of maximal effect support the observations of others [18b, c] that the cardiac effect of quinidine is not directly proportional to its blood levels.

Our observations on the effects of intramuscular administration of quinidine lactate in subjects with cardiac arrhythmias generally parallel accumulated past experience with oral use of quinidine, the only major difference being the more rapid onset of maximal effect. In 22 episodes of cardiac arrhythmia reversion to normal sinus rhythm occurred in 15 instances following single or multiple parenteral doses of quinidine. Only in those cases that did not revert to normal sinus rhythm following a single dose of quinidine was it possible to observe the times of maximal effect, since restoration to normal rhythm may occur before peak effect is attained.

Two of the eight subjects with supraventricular tachycardia did not follow the "all or none law" and showed progressive slowing of the auricular rate with each succeeding dose of quinidine lactate. In these subjects the maximal effect of each dose as estimated from slowing of the rate was attained in about one hour. Among patients who had auricular fibrillation and auricular flutter with sufficiently distinct oscillations to allow measurement of auricular rate, a maximal response to each of repeated doses occurred within a half hour in persons with auricular flutter and within one hour in those with auricular fibrillation. Progressive slowing of the ventricular rate occurred in one patient with ventricular tachycardia following each of two repeated hourly intramuscular doses of quinidine; the maximal effect of each dose was obtained within one hour.

The maximal effect of oral administration of quinidine in auricular fibrillation has been described as occurring between two and four hours,[15] whereas by the intramuscular route the maximal response occurred between 30 and 60 minutes in our patients with auricular fibrillation, auricular flutter, supraventricular tachycardia and ventricular tachycardia.

The occurrence of pseudo ventricular tachycardia in two subjects with 2:1 auricular flutter (cases 47 and 48) following the intravenous administration of 0.65 Gm. of quinidine lactate merits special note. At the time of pronounced slowing of auricular rate, 1:1 auriculoventricular response occurred. The fatiguing effects of the rapid ventricular rate during these episodes of 1:1 auricular flutter resulted in abnormal widening of the QRS complexes, so that the tracings could be easily confused

15. Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observations upon the Action of Certain Drugs upon Fibrillation of Auricles, Heart **9**:207-265, 1922. Wégria, R.: Intensity and Duration of Action of Quinidine Sulfate in Auricular Fibrillation and Flutter as Measured by Rate of Circus Movement, Am. Heart J. **35**:787-792, 1948.

with ventricular tachycardia. The exact nature of this train of events was made apparent by the fortuitous occurrence of these transitions on the tracings obtained in case 47 (fig. 3). It is likely that some reported cases of ventricular tachycardia occurring during the treatment of auricular fibrillation with quinidine are in reality instances of pseudo ventricular tachycardia caused by the mechanisms described above.

Our observations that the maximal cardiac response to a single intramuscular dose of 0.65 Gm. of quinidine is obtained in 30 to 60 minutes

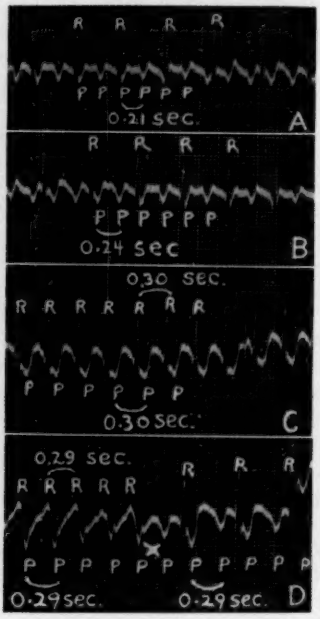

Fig. 3 (case 47).—Pseudo ventricular tachycardia following intravenous administration of quinidine. All tracings shown are lead II. *A*, control showing 2:1 auricular flutter, a P-P interval of 0.21 second and an auricular rate of 286 per minute. *B*, two minutes after administration of 0.65 Gm. of quinidine intravenously. P-P interval is increased to 0.24 second and auricular rate slowed to 250 per minute. *C*, 10 minutes after quinidine administration; P-P interval measures 0.30 second, and auricular rate is 200 per minute, with 1:1 ventricular response. *D*, 12 minutes after quinidine administration; pseudo ventricular tachycardia produced by 1:1 auricular flutter with intraventricular block; resumption of 2:1 flutter with normal QRS complexes occurs at X.

and maintained at least four hours suggest the following schedule for multiple dosage.

When a rapid therapeutic response is desirable, as in paroxysmal tachycardia, and has not been achieved with a single dose, hourly adminis-

tration is indicated, since there will be little, if any, increment in effect after one hour. In instances in which the necessity for speed of therapeutic response is less urgent, as in chronic auricular fibrillation, an intramuscular dose can be repeated at intervals of three to four hours, since the maximal effect of a preceding dose persists at least that length of time. Thus, ample opportunity is afforded to observe the therapeutic response or toxicity of any single dose.

SUMMARY AND CONCLUSIONS

Quinidine lactate (0.65 Gm.) administered intravenously within several minutes produces a maximal cardiac effect, as determined by changes in QT_c, within 15 minutes. The magnitude of effect is greater than that attained with identical doses administered orally or intramuscularly. However, the toxic effects of quinidine lactate given intravenously make its therapeutic use hazardous.

Pseudo ventricular tachycardia occurred in two subjects with auricular flutter following the intravenous administration of 0.65 Gm. of quinidine lactate.

Quinidine lactate (0.65 Gm.) administered intramuscularly is no more toxic than quinidine given orally in similar doses. A maximal cardiac effect in subjects with regular sinus rhythm (normal and abnormal hearts) is attained in about 30 minutes. The duration of peak effect is between two and four hours in subjects with normal hearts and at least six hours in those with abnormal hearts. At 24 hours a small but significant quinidine effect persists.

Of 22 subjects with cardiac arrhythmias 15 were restored to regular sinus rhythm by single or multiple parenteral doses of quinidine, although our efforts were not primarily directed toward treatment of the arrhythmias. The maximal effect as estimated by slowing of the ectopic pacemaker occurs between 30 and 60 minutes following the intramuscular administration of quinidine lactate.

Our observations suggest the following time schedule for intramuscular administration of quinidine: When rapid therapeutic effect is important, hourly administration is indicated; when necessity for speed in therapeutic response is less urgent, administration should be at intervals of three to four hours.

Progress in Internal Medicine

ANNUAL REVIEW OF RHEUMATIC DISEASES

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A CONSIDERATION of advances in rheumatology, at this time, is subject to several restrictions. The results of investigative therapy with new agents can be stated only in tentative form. The fluid developments, like a rapid current, are more difficult to penetrate for a distinction between substance and shadow. But even a critical evaluation of contemporary research in this field remains a stifling exercise, unless one can project it onto the fundamental purpose of medicine, the prevention or cure of disease. Despite the hazard of premature interpretation, therefore, this report includes the demonstration of some clinical guideposts, however soon they may be reset. More disturbingly, the confines and divisions of rheumatism today are not nearly so certain as they appeared to be when attention was concentrated on the articular manifestations of the arthritides. Thus, one finds less justification than ever for isolating rheumatology as a medical specialty. Rather, a report on rheumatic diseases concerns a matter of natural interest to all physicians, notably to internists.

RHEUMATISM AND PUBLIC HEALTH

Incidence and Economic Liability.—The importance of these subjects is not fully reflected in the number and quality of statistical studies published. The British Empire Rheumatism Council (Horder) has estimated the number of adults in the Empire suffering from rheumatic diseases at more than 1,000,000, or one in 50 of population. The financial burden in sick pay, lost wages and cost of treatment among insured workers alone is £17,000,000 per annum, but this accounts for only one third of the population. The total annual cost of these illnesses to the British nation is calculated to be in excess of £30,000,000. The American Rheumatism Association in its "Primer on the Rheumatic Diseases" has published figures for this country based on a survey made by the United States Public Health Service. These indicate that over 7,500,000 persons in the United States, or more than 1 in 20 of population, are afflicted with some form of rheumatism. The incidence of new cases of rheumatic fever alone, among persons between 5 and 24 years of age, is estimated at 30,000 annually (Hill and others). The total cost of this category of illnesses exceeds $750,000,000 annually in terms of expenditures for medical purposes, lost wages and direct financial subsidies.

One must remember that the data concerning both incidence and economic loss are approximations calculated from relatively small samples. There is undisputed need for better statistical information. However, the task of collecting valid material has been impeded by the lack of uniform diagnosis. In this and other respects the "Primer on the Rheumatic Diseases," revised last year by a committee of the American Rheumatism Association, and listing 30 different entities of primary or secondary arthritis, should be useful.

Epidemiological Studies.—Statistical studies prove close correspondence in geographic distribution of streptococcic pharyngitis and rheumatic fever, as well as parallelism of seasonal occurrence. In the population at large approximately 5 per cent of patients with streptococcic pharyngitis may contract rheumatic fever later (Hill and others). Buchan (1950 *b*) tabulated monthly aggregates since 1921 of deaths due to rheumatic fever, scarlet fever and acute nephritis and showed coincidence in the secular trend of scarlet fever and acute rheumatism. Seasonal influences are clearly demonstrated, as scarlet fever reaches a peak in January, followed approximately one month later by a peak for rheumatic fever and nephritis. The author suggests that streptococci contained in raw milk may be the cause of prerheumatic infection in many areas of the world and cites epidemiological observations on an isolated community in the Yukon, where only canned or powdered milk is used. During 14 years no typical case of rheumatic fever has occurred there, although the community counts about 350 children under 13 years of age (Buchan, 1950 *a*). The effect of segregation on the spread of beta hemolytic streptococci was not considered here. A correlation between death from rheumatic fever and climate was demonstrated in a survey of Texan communities (Heyer and others). The death rate is higher in colder counties than in those where mild or subtropical winter weather prevails. From statistics of life insurance holders, it appears (Wheatley) that the mortality rate from rheumatic heart disease decreased by 22 per cent between 1920 and 1940 and by 85 per cent in the seven years following. The accelerated decline in the latter years may be due to the increased use of antibiotics and sulfonamides in the treatment of streptococcic infections. This surmise is strengthened by reports for England and Wales (General Register Office), where an opposite trend obtained during the postwar years. Concomitantly, a low mortality rate due to rheumatic fever has been found among 1,042 patients surviving puberty and followed for up to 30 years (Wilson and Lubschez). The mean age of onset in this group was 6.5 years, and death was due to rheumatic heart disease in 75 per cent and to subacute bacterial endocarditis in 10.2 per cent of the patients. The influence of modern prophylactic therapy and of improved treatment for subacute bacterial endocarditis is not reflected in this study.

The familial incidence of various rheumatic ailments has interested many investigators. Tegner and Lloyd observed ankylosing spondylitis in all three children of one family, two boys and 1 girl. As this disease may be mild or disguised by atypical symptoms, it is likely to be obscured in many family histories. The familial trend of rheumatoid spondylitis was substantiated by Rogoff and Freyberg, who found a positive family history in 140 cases. Stecher, Solomon and Wolpaw observed that rheumatoid arthritis occurred in the fathers, mothers and sisters of rheumatoid patients in a significantly higher proportion than it did in the relatives of patients with spondylitis or in the control patients with degenerative joint disease, gout and miscellaneous nonarticular ailments. Spondylitis occurred in the brothers and sisters of patients with spondylitis more than it did in any other group, and rheumatic fever occurred much more frequently in the patients with rheumatoid arthritis or with spondylitis than in any other group. It may be recalled here that Stecher (1948) demonstrated a hereditary susceptibility to Heberden's nodes, a prime manifestation of degenerative joint disease. Stecher, Hersh and Solomon investigated the hereditary aspects of gout and hyperuricemia. An analysis based on 248 serum uric acid determinations on 201 members of 44 gouty families and on 1,024 serum uric acid determinations on 961 patients examined routinely at a general hospital showed that about one eighth of the relatives of gouty persons have unsuspected hyperuricemia. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male and about 12 per cent or less in the female. Not a single daughter among 45 tested was found to have hyperuricemia. Eighteen per cent of 11 mothers, 17 per cent of 24 brothers, 21 per cent of 24 sisters and 15 per cent of 33 sons had elevated levels of blood serum uric acid. No female relative below the age of 50 was affected. It has not been determined when this biochemical abnormality first appears or how it is related to symptomatic gout. The influence of various environmental factors, such as trauma and shock, in the precipitation of gouty arthritis is common clinical knowledge, but studies among Hindus and Mohammedans in South Africa (Finn) suggest that rules prescribing abstinence or vegetarianism do not modify the incidence of gouty arthritis. This is governed principally by a hereditary diathesis. Statistical confirmation of an empirically accepted characteristic of these rheumatic diseases has thus been secured. The familial predisposition to rheumatoid arthritis and spondylitis, at the same time, is shown to be specific for neither of the clinical entities, and a considerable overlap with that to rheumatic fever is indicated (Short and others).

The importance of industrial hygiene in various rheumatic diseases has gained recognition. A challenging contribution to this subject was made by Agate. He determined that among 279 workers who

polished metal castings with rotary tools, there were 234 men and 24 women afflicted with Raynaud's syndrome. The dominant hand was attacked less often, later and less severely than the subordinate, in which the ring and middle fingers were most frequently involved. These patients were followed for 2.5 years, at which time the disease appeared to be stationary in one half of the patients, whereas it had progressed in 36 per cent. The data here presented permit of no definite conclusions concerning the effect of occupation on an ill defined complex of symptoms. Yet there has been a sufficient number of reports on the development of vascular obliterative lesions with degenerative articular disease to warrant more comprehensive studies and animal experiments on the influence of vibratory trauma to blood vessels and skeletal structures.

Prevention.—For a group of diseases which are the commonest cause of crippling and which require exorbitant expenditure of public and private funds, the development of preventive measures is clearly an important task. No effective prophylaxis has been found against rheumatoid arthritis, despite attempts to avoid or eliminate the various suspected precipitating factors. Efforts to prevent deformation and wasting have been somewhat more successful, but their application is limited by the high cost and the lack of facilities, as well as lack of professional personnel. At present, there is growing interest in the possible use of pituitary adrenocorticotropic hormone (ACTH) and cortisone for the control of connective tissue contractures in rheumatoid arthritis and of the endocardial lesions in rheumatic fever. An appraisal of results must wait for several years of observation. However, the use of sulfonamides and penicillin in the prophylaxis of rheumatic fever has proved to be of value (Cruickshank; Rutstein; Pitt). At a special public school for children with rheumatic heart disease in Chicago, 126 pupils were observed for three years (Kohn and others). One half of the group was given penicillin orally in daily doses of 800,000 units throughout the first week of every month of the school year. This prevented throat infections due to hemolytic streptococci and recurrences of rheumatic fever, which affected 11 and 19 per cent of children in two untreated series. Denny and his co-workers presented a thoroughly controlled study on Air Force personnel at Fort Warren, Wyo. All patients had exudative pharyngitis, bacteriologically proved to be caused by group A beta hemolytic streptococci in 80 per cent of the cases. Among 798 patients treated with penicillin, mostly within 60 hours, two acquired rheumatic fever; of 804 controls receiving no specific therapy, 17 had rheumatic fever. The following treatment schedule was employed: Three hundred thousand units of crystalline procaine penicillin G suspended in peanut oil was administered intramuscularly as soon after admission as possible and again in 48 hours. Six hundred thousand

units was given 96 hours after the initial dose. This treatment likewise suppressed the antistreptolysin titer and eradicated streptococci in many cases. The best evidence to date shows that it is rational to treat with penicillin all patients having streptococcic infections, assuring an adequate and continuous penicillin level in the blood for one week to 10 days. The beneficial effect of sulfonamide prophylaxis in children with proved rheumatic disease was corroborated in a clinical and bacteriologic study on 211 patients, with a control group of 337 children (Rubbo and others; Stokes). The two series were closely matched and studied simultaneously for 971 and 505 person years, respectively. There was a recurrence rate of 3.2 per cent in the treated group, compared with 11.8 per cent in the control group. In the former group a significant reduction of group A hemolytic streptococci occurred. Resistance was tested on 669 strains isolated from both groups. It developed in 29 per cent of the group A strains isolated from the treated subjects and in 6 per cent of those derived from the controls. Minimal toxic reactions were encountered. Neither these reactions nor development of resistant strains was considered a contraindication to prophylaxis (Krumwiede).

Rehabilitation.—Attempts to restore persons disabled by chronic rheumatic diseases to social and economic activity have not been undertaken systematically or on a large scale in this country. We may benefit in the planning of such a program by the experiences of "Re-Employ Limited," a British industrial organization which operates factories and employs in productive work all men and women registered at an employment exchange as disabled to such an extent that they cannot expect to obtain and hold work in open industries. This project includes at present 240 persons with rheumatism. A separate home work team is active in 10 districts, but this branch has difficulty in finding a suitable, uniform and marketable product (Venn). The rehabilitation of persons with chronic arthritis may be delayed and hindered by the development of a dependent attitude readily engendered in clinical practice. That this concern does not necessarily apply to rheumatic children spending a long time in a sanatorium appears from a report on 100 young patients studied for their adaptation to the institutional environment (Taran and Hodsdon). It was concluded that such an experience did not seriously interfere with the psychological development of children and adolescents, nor did prolonged separation from home for sanatorium care appear to disturb the integrity of family life. Perhaps this result measures to a lesser degree the psychological effect of long-continued illness with institutional confinement than it does the benefits derived by sick and often underprivileged children from enlightened management and optimal treatment. In a group of children with rheumatic fever there was a larger proportion of emotional disturbances than in a group of physically well unselected children. This maladjustment did not follow any character-

istic pattern and appeared related to the problems of the child before the rheumatic process began. Josselyn proposes that the effect of the physical illness on psychic stability results from decreased capacity to deal with problems aggressively and to defend against aggression by others. The author points to the importance in rehabilitation of resolving neurotic anxiety and of causing the patient to accept the dictates of limited living.

Effective control of rheumatism as a problem in public health remains a major and urgent task. At best, the agencies concerned with this undertaking have begun to define their objectives. Methods of achieving them are poorly understood as yet, but a few promising steps have been taken. In the Arthritis and Rheumatism Foundation have been focused the concerted educational efforts of the medical profession and of private and public health agencies. This voluntary organization, with the American Rheumatism Association, has sponsored legislation to create an Institute for Arthritis and Metabolic Diseases. It will be designed to provide a means for intensive research into the causes of rheumatic diseases and into their epidemiological hygiene.

PATHOPHYSIOLOGY OF CONNECTIVE TISSUE

Structure and Function.—During the last decade clinicians have become increasingly aware that many rheumatic diseases are systemic in nature. Their manifestations may appear in a wide variety of organs. An appropriate but tentative concept explains the diffuse pathological involvement in rheumatic disorders as a multifocal nonspecific inflammation of connective tissue. Earlier studies on the physiology of articular structures have shown that all major components of a joint derive from mesenchyma and represent various modifications of connective tissue. Great importance, therefore, attaches to studies ascertaining the structure and function of this element. These have recently been summarized by Bensley and Ham. Connective tissue normally has the dual function of support and nutrition. It requires a high proportion of intercellular substance characterized as a nonliving material which is stronger than living cells. All blood and lymph vessels are confined to connective tissue. As most living cells are not in contact with capillaries, nutrition must be mediated through the connective tissue matrix. Presumably, tissue fluid emerging from the capillaries as a dialysate of blood plasma is diffused through the amorphous ground substance to furnish nutritive materials and, after metabolic exchange, reenters the venous and lymph capillaries. The amorphous intercellular substance appears specialized to permit nutritive diffusion between capillaries and cells. This ground substance, which contains a mucopolysaccharide, presumably is elaborated by fibroblasts. They also produce the formed type of intercellular material, such as reticular, collagenic and elastic fibers. Under abnormal conditions, principally the connective tissue

cells are concerned with specific defense, for instance, against infection, but the intercellular substance may also act as a barrier to foreign agents. Thus, connective tissue *in toto* becomes the "arena of inflammation."

This rational, and in part hypothetical, description is based on histological examination of stained tissues and other, indirect evidence. Despite much refinement in histochemical methods, their specificity for the various components of ground substance is open to doubt. Some of these limitations in morphological diagnosis of connective tissue structures have been overcome by the use of the electron microscope, which permits characteristic structural details of collagen and other fibrous proteins to be identified (Gross and Schmitt). The suboptical structure of the collagen fiber has been described as a bundle of fibrils embedded in an amorphous matrix of acid polysaccharide and protein. Normal collagen exhibits a consistent pattern of cross banding. The new technic promises to be particularly helpful in the study of "fibrinoid" and of cloudy swelling, both ill defined and commonly seen in collagen diseases. Electron microscopy has served to demonstrate that hyaluronic acid, a protein carbohydrate compound of the matrix, is a highly polymerized substance whose macromolecular units are sufficiently long and asymmetrical to suggest the property of viscosity (Gross). One may anticipate that this advance in method will lead to better understanding of the normal articular structures and will aid in defining those changes in intercellular colloids which are incident to physiological aging.

Like previous investigators, Davies has characterized the synovial membrane as a relatively undifferentiated connective tissue organ, but he denied the presence of free nerve endings, repeatedly described in proximity to subintimal blood vessels. He observed that in a living unanesthetized person, the membrane was insensitive to touch, pricking and pinching, whereas tugging produced a poorly localized painful sensation. The assertion that the synovial cells produce mucin is compatible with well known physiological facts but has not been proved.

Biochemical studies on the physiology of matrix (Meyer and Rapport) indicate the presence of five distinct mucopolysaccharides in mesodermal tissue, one of which, a sulfate-free ester, is hyaluronic acid or mucin. Three of the four sulfate-containing esters are composed of chondrosamine, hexuronic acid and ester sulfate. They differ in optical rotation and susceptibility to hydrolysis by the enzyme hyaluronidase. Cartilage yields one of these, chondroitin sulfate A, but not hyaluronic acid which is the mucopolysaccharide of synovial fluid. Normal adult loose connective tissue contains little or no hyaluronic acid, but this is present abundantly in subcutaneous tissue and in embryonal mesenchyma. If one accepts the chemical specificity of certain stains, one may surmise that with increasing age there is increased production of chondroitin sulfate B at the expense of hyaluronic acid, whereas young mesenchymal

cells appear to produce hyaluronic acid and chondroitin sulfate C. According to Follis, the phosphatase activity in growing cartilage varies with the degree of differentiation. The enzyme is detectable in the zone of undifferentiated cells, and its concentration increases with the state of hypertrophy of chondrocytes.

Degenerative Processes.—The relationship of endocrine glands to the aging of articular cartilage was studied in laboratory animals (Silberberg and Silberberg). Degenerative and hypertrophic changes occurred spontaneously in aging mice, the lesions being histologically indistinguishable from those seen in man. Certain strains appeared to be predisposed to the development of degenerative lesions at an earlier age and to a severer degree than others. The administration of male and female sex hormone delayed the appearance of senile catabolic changes and decreased their incidence. Conversely, the administration of anterior hypophysial extracts or the removal of sex glands hastened the onset. Interesting suggestions arise from this work. If the results could be applied to human degenerative joint disease, one would want to explore further the implied etiological role of anterior pituitary gonadotropins and to separate, if possible, their effect from that seen in acromegalic joint disease. Endocrine causes were also incriminated in certain extra-articular rheumatic syndromes. Copeman has frequently found anatomic evidence of adipose tissue herniating through a fibrous capsule. On the basis of these observations, it is surmised that glandular factors have caused retention of fluid, leading to the protrusion of fatty tissue through its fibrous covering and to tension and pain. The histological observations are nicely documented, but their clinical significance and, even more, their physiological basis remain in doubt.

A differentiation between osteophytosis of the vertebral bodies and osteoarthritis of the spine was attempted by Collins. The former is considered the result of collapse, degeneration or distortion of one or more intervertebral disks. In this condition the small diarthrodial joints of the vertebral column may be normal. The latter is designated as a typical example of osteoarthritis initiated by degeneration of articular hyaline cartilage. The dissociation here reported is indeed a common observation. It does not prove an essential difference in the pathogenesis of the two processes.

Rheumatoid Lesions.—As the concept of rheumatoid arthritis has widened into that of a systemic disease, many extra-articular tissues have been scrutinized for their involvement in this process with more or less specific pathological changes. Graef and his co-workers reported gross deformities of the heart valves in 29 of 66 patients at autopsy, only one of these having a history of antecedent rheumatic fever. Mitral stenosis was present in one person. In two patients the endocardium contained a granulomatous zone of interstitial collagenous

necrosis, indistinguishable from that seen in subcutaneous rheumatoid nodules. Pericarditis was present in one-half the patients. Chronic inflammatory interstitial myocarditis occurred in seven, and 40 per cent of the patients showed perivascular fibrosis of significant degree. The coronary arteries of two patients showed lesions similar to those of periarteritis nodosa. In more than 40 per cent of 150 necropsies on patients with rheumatoid arthritis, cardiac lesions indistinguishable from those seen in rheumatic fever were encountered (Rosenberg). Such changes included scarring and deformity of heart valves, with severe myocardial and pericardial damage. Inflammatory changes were also detected in striated muscle of many patients with rheumatoid arthritis (Horwitz, 1949 *a*; Kestler; Sokoloff and others). Morrison, Catoggio and Bauer observed no particular relationship between the presence of these endomysial and perimysial lesions and the degree or duration of rheumatoid activity, the age of the patient, the anatomic position and the condition of the muscle. The paravascular foci of small round cells appeared to have no specific diagnostic features and resembled those seen in disseminated lupus erythematosus, dermatomyositis, rheumatic fever and other entities in the group of collagen diseases. Nerve tissue from the spinal cord and from sympathetic ganglions showed these lesions in about 75 per cent of specimens, situated usually in the perineurium. The sympathetic ganglions were also affected by cellular infiltrations, both along the course of the fibers and within the capsule. In addition, some specimens showed slight alterations in the myelin sheaths and axons of the peripheral nerves, with retrograde degeneration of anterior horn cells of the spinal cord. Although not pathognomonic, these lesions were more pronounced than those which occur with aging alone. Somewhat greater specificity in the nature of palisading connective tissue cells surrounding a necrotic focus was detected by Kellgren and Ball in biopsy specimens from tendon sheaths of rheumatoid subjects and by Horwitz (1949 *b*) in subcutaneous nodules containing lipid. Abnormalities of blood vessels have recently been seen in a small percentage of rheumatoid muscle tissue (Bunim). This particular type of arteritis was absent from 111 samples of striated muscle of patients with other forms of rheumatism, subacute bacterial endocarditis and miscellaneous diseases. Although without distinctive histological characteristics, it is described as an inflammatory infiltration of the adventitia and occasionally of all coats of small arteries. Necrosis of collagen and intramural vascularization are not prominent features of this lesion. If confirmed, this observation enlarges the scope of pathological study of rheumatoid tissue, although necrotizing angiitis has previously been described in the rheumatoid synovial membrane (Bauer and others; Soeur).

Collagen Diseases.—The increased volume of pathological studies on biopsy and necropsy material from patients with various rheumatic dis-

eases has led to a more complete understanding of the abnormal physiology of connective tissue and, at the same time, has furthered research into the relationships of rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma. While it is possible to distinguish clinically in most instances these entities gathered under the purely topologic designation "collagen diseases," the borderlines of tissue changes are occasionally diffused and overlapping (Bauer and others; Curtis and Horne; Lowman). The vascular lesions of disseminated lupus may appear similar, if not identical, to those of periarteritis. Conversely, the discovery of Aschoff bodies in a patient with typical periarteritis complicates the problem of differential diagnosis within this group of diseases. The systemic spread of periarteritis nodosa was well demonstrated in a number of studies from the Mayo Clinic (Lovshin and Kernohan; Parker and Kernohan; Ralston and Kvale; Sweeney and Baggenstoss; Wold and Baggenstoss), showing characteristic lesions in the vascular apparatus of the lungs, the central nervous system, the gastrointestinal tract, the kidneys and the peripheral nerves. Further evidence was accumulated to define a pathognomonic feature of acute disseminated lupus in describing the L. E. cell in the plasma and bone marrow (Hargraves; Haserick; Haserick and Bortz). Whereas some workers suggest that this represents an immunologic phenomenon and postulate an etiogenic gamma globulin, Gueft describes the staining reactions of these cells by means of histochemical technics as indicating depolymerization of nucleic acid.

Serologic Changes.—In contrast to normal serum proteins in rheumatoid spondylitis (Paul and Routh), depression of the albumin to globulin ratio is a common feature of the pathophysiology of rheumatic fever (Knapp and others) and of rheumatoid arthritis (Wallis). Blood specimens selected for their low ratio on the basis of chemical fractionation were analyzed by electrophoresis. The serum of four patients showed increases in the alpha and, chiefly, the gamma components. Three of the four specimens also showed a T component not previously reported in rheumatoid arthritis. The latter, like the gamma fraction, is attributed to immunization. Specimens from 10 patients were also examined by an immunologic method utilizing rabbit antihuman gamma globulin serum. This test showed gamma globulin values which averaged more than twice the normal content of this protein. In most respects, this study corroborates previous observations. The method is superior for the measurement of plasma protein changes to that which uses the differential plasma viscosity (Lawrence; Houston and others). The synovial fluid proteins are altered in the same direction (Ropes and others), and the permeability of the membrane is increased. There appears to be an increased production of low polymer hyaluronate

(Meyer and Rapport). This was interpreted as indicating that in rheumatoid arthritis production of abnormal mucin rather than increased breakdown of normal mucin is responsible for the changes in the synovial fluid.

In rheumatic fever within a few weeks of the onset of group A streptococcic infection, there occur in the serum of most patients antibodies against different general classes of streptococcic antigens (Harris and others). The antistreptolysin O, antistreptokinase and antihyaluronidase form in response to extracellular antigens. The occurrence of type specific bacteriostatic antibodies against multiple types of group A streptococci indicates previous heterologous infections and suggests that recurrences of rheumatic fever may actually represent a new attack attributable to different types of group A streptococci (Swift, 1949 *b*).

Nutrition.—The role of dietary factors in the pathogenesis of rheumatoid arthritis still appears uncertain. Bayles, Palmer, Massod and Judd studied the vitamin B excretion in 40 patients by fasting and saturation tests. There appeared to be no correlation between the duration or severity of the rheumatoid process and the urinary excretion of vitamin B components. Recovery of thiamin, riboflavin and nicotinic acid was not essentially different in patients and controls. Acetylation of paraaminobenzoic acid and sulfadiazine in eight rheumatoid patients was comparable to that in eight controls and was not materially influenced by the oral administration of 10 mg. of calcium pantothenate daily for prolonged periods (Kuhl and others). Whereas the hypochromia of the blood in rheumatoid disease has been refractory to nearly all antianemic measures, the hemoglobin concentration can be raised by intravenous injection of iron (Clark; Sinclair and Duthie). The therapeutic potential and toxic range of this procedure await clarification.

Effect of ACTH and Cortisone on Pathophysiology.—Investigations into the pathogenesis of rheumatic diseases received an incomparable stimulus from the discovery by Hench, Kendall, Slocumb and Polley (1950; 1949 *a*) that the clinical manifestations of rheumatoid arthritis could be controlled by administration of 17-hydroxy-11-dehydrocorticosterone (cortisone) and by pituitary adrenocorticotropic hormone (ACTH). The unprecedented opportunity afforded by these new tools of research was quickly recognized (Spies and Stone, 1950). Despite their limited supply, and owing in large measure to the prudent method of distribution, a mass of clinical and laboratory data was available by the end of 1949. Thorn and his co-workers (Thorn and Bayles; Thorn and others, 1949), who had for a number of years studied the metabolic action of corticoids and ACTH, summarized their own work and that of others in a review of pituitary-adrenal function and its possible relationship to rheumatic diseases. They suggested that the majority of patients with such mesenchymal disorders possess a normal cortical reserve but may be

incapable of evoking it spontaneously. Given a sudden increase in the level of circulating cortisone, either by direct administration or by stimulation of the adrenal cortex with ACTH, the nonspecific inflammatory reaction of several rheumatic diseases appeared favorably altered. The mechanism of this change remains unknown.

Metabolism and Blood Constituents.—The metabolic effects, however, as far as electrolyte and nitrogen balance are concerned were soon elaborated by Sprague and his colleagues, with whom subsequent workers remained in essential agreement. A negative balance for nitrogen and potassium followed the administration of ACTH in a daily dose of 100 mg. for 12 days. Simultaneously, there was marked retention of sodium and chloride superseded by increased excretion of these ions, with the development of hypochloremic, hypokalemic alkalosis. In antirheumatic doses, given up to one month, cortisone caused a significant alteration in the electrolyte concentration and nitrogen balance of the plasma. Occasionally, the plasma potassium was slightly lowered. Administration of 200 mg. of cortisone acetate for 12 to 18 days effected negative nitrogen and potassium balances regularly and had a variable influence on excretion of sodium and chloride. Most frequently, there was initial retention, followed by increased excretion, with development of hypochloremic and hypokalemic alkalosis. The blood electrolytes returned to normal values after treatment with the hormone was discontinued. The catabolic effect of cortisone acetate was not offset by administration of 10 mg. of estrone in a woman with artificial menopause, but 25 mg. of testosterone propionate prevented increased potassium and nitrogen excretion. The authors were not prepared to explain the favorable clinical effects of ACTH or cortisone on rheumatoid arthritis by the metabolic action of these hormones. A number of other studies concerning the effect of ACTH on carbohydrate and protein metabolism (Holbrook and others; Proceedings of First Clinical ACTH Conference) have not so far been clearly related to the antirheumatic effect. The same must be said about the hematological response to these drugs (Hain and Wilson). Four hours after a single 25 mg. dose of ACTH, there occurs a sharp drop in circulating eosinophils, ranging from — 39 to — 100 per cent, with reticulocytosis, a rise in the total neutrophils ranging from + 5 per cent to + 67 per cent and a drop in lymphocytes ranging from — 19 to — 55 per cent.

Tissue Response.—As hyperplasia of lymphatic tissue is a common pathological finding in rheumatoid arthritis, the destructive effect of cortisone and ACTH on both lymph nodes and circulating lymphocytes is of particular interest. In this respect, earlier observations have been confirmed, although a concomitant rise in antibody titer has not been conclusively demonstrated. Plotz and his colleagues (Plotz, Blunt, Lattes and Ragan; Plotz, Howes, Blunt, Meyer and Ragan; Ragan,

Howes, Plotz, Meyer and Blunt; Ragan, Howes, Plotz, Meyer, Blunt and Lattes) observed delayed repair of experimental wounds in rabbits treated with cortisone as compared with controls. The animals given the injection showed strikingly less healing, apparently due to absence of fibroblasts and capillary proliferation, although epithelium was regenerated to a moderate degree. The difference from the normal was particularly striking in animals receiving 25 mg. daily of cortisone but could also be noted in those with a daily dose of 7.5 and 5 mg. Observations were made on the healing of experimental fractures under the influence of cortisone as compared with untreated controls; in the hypercorticoid animals absorption of the traumatic hematoma and callus formation were greatly delayed (Blunt and others). The suggestion was advanced that the beneficial action of cortisone and ACTH in the mesenchymal diseases may be related to the depressive effect on host reactivity to noxious agents. Observations on clinical subjects receiving surgical wounds while under treatment with the hormones have, however, not been unanimous in regard to healing and repair (Proceedings of First Clinical ACTH Conference). The size and microscopic appearance of subcutaneous rheumatoid nodules have not been consistently affected (Clark and others; McEwen); in fact, new nodules have appeared in some patients during therapy. The scleritis and episcleritis of rheumatoid disease were diminished (Mann and Markson; Talkov, Colpoys, Davis, Papper and Feinberg), and the histological synovitis was reduced, as shown in biopsies before and during treatment (Hench and others, 1950). Both agents decreased the permeability of the synovial membrane to diffusible dyes (Leifter, Baeder, Begany and others; Leifter, Warter and Fitch). The electric potential between the inner surface of the articular cavity and a subcutaneous point in anesthetized dogs was reduced by as much as 60 per cent after intramuscular injection of 25 mg. of ACTH. This also applied to unanesthetized human subjects with rheumatoid arthritis and healthy controls (Reed and others).

Immune Reactions.—The ameliorative effect of ACTH on inflammation in a variety of rheumatic diseases and in certain allergic conditions suggested application of the substance to the Shwartzman phenomenon (Soffer and others). Animals receiving adrenocorticotropic hormone prior to the preparatory injection reacted in the same manner as the controls, but the animals given 12.5 mg. per animal of ACTH by intramuscular injection preceding the test dose had no reaction in eight of 10 cases. Depression of experimental hyperergy (Berthrong and others) and inhibition of tuberculin sensitivity have been reported (Stoerk), but the evidence concerning serologic antibodies is incomplete.

It appears quite probable, therefore, that the antirheumatic effect of these hormones is in part exerted by their action on connective tissue

constituents directly. Whether the vascular apparatus alone is affected in this mechanism, or whether it concerns connective tissue cells and ground substance as well, cannot yet be stated. The observation that under the influence of ACTH the mucin of rheumatoid synovial fluid tends toward normal (Clark and others) is not of critical significance to this point. It is doubtful that the anti-inflammatory action occurs through interference with the effect of histamine (Bordley and others). Several physiological observations cannot yet be appraised in their possible significance to rheumatic diseases. Certain corticosteroids have an anti-hyaluronidase effect on connective tissues (Opsahl; Seifter, Baeder and Begany; Shuman and Finestone; Winter and Flataker). The increased inhibition of the spreading factor in the serum of patients with rheumatic fever (Dorfman and Moses; Dorfman and others) is definitely reduced after treatment with ACTH, paralleling the decrease in sedimentation rate and improvement in the clinical course. These findings may be used to advantage in the experimental study of arthritis, but they possess only hypothetical significance when applied to the pathogenesis of rheumatic disease in human beings (Epstein and others; Harris and Friedman). Preliminary studies have indicated that several steroid hormones exert an analgesic effect (Thorn and others, 1949). It seems clear, however, that only a fraction of the antirheumatic properties of cortisone could be ascribed to this pharmacologic action.

Uric Acid Metabolism.—Hellman demonstrated that during the administration of ACTH the urinary excretion of uric acid is increased. Robinson and his co-workers corroborated the rise in uric acid excretion and the fall in blood urates of gouty patients treated with ACTH. While these authors considered that gout is characterized by a low excretion of 17-ketosteroids and that the adrenal cortex of gouty patients may be caused to respond readily to stimulation, Wolfson and his colleagues postulated that an abnormal male hormone of the adrenal cortex may be responsible for the relative insufficiency of 11-oxysteroids leading to acute gouty arthritis. The excretion of uric acid may be increased as much as 80 per cent and the blood urate concentration decreased as much as 30 per cent by ACTH administration. It appears, however, that the hormone-induced urate diuresis does not exceed and need not equal that which accompanies large doses of salicylates. Benedict and his associates have arrived at the tentative conclusion that the action of ACTH in reducing the serum uric acid concentration without changing its dilution, as measured by the radioactive isotope of nitrogen, N^{15}, indicates reduced reabsorption by the renal tubular epithelium. In gouty arthritis, as in a variety of rheumatic diseases, there may also occur a nonspecific effect of ACTH, inhibiting the inflammatory reactions of synovial tissues.

CLINICAL MANIFESTATIONS

Osteoarthritis.—The course of primary degenerative joint disease or osteoarthritis is not well understood, despite the extraordinary commonness of that disorder and despite much progress in elucidating its pathogenesis. There is need for better correlation between lesions and symptoms and their relationship to various precipitating factors, such as trauma and menopause. Several reasons for this deficiency in clinical definition can be seen. It is difficult to separate the idiopathic form from secondary degenerative changes. There is no specific test at the early stage of the disease. The criteria which are usually taken for diagnostic, such as gross physical changes and roentgenologic excrescences at the periarticular margins, occur late in the disease and represent a secondary reaction of articular tissues. At present, the early diagnosis of degenerative joint disease depends often on exclusion of other rheumatic processes. Chronic observation is but rarely successful in this self-limited disorder. To the gathering of such clinical data, the analysis by Stecher, Beard and Hersh of the incidence of degenerative joint disease of the fingers marks an auspicious beginning. These authors determined that the development of Heberden's nodes depends on hereditary predisposition and an intact and normally functioning nerve supply to the hand and fingers. Secondary factors include race, age and menopause. There is a significant correlation between the onset of Heberden's nodes and the menopause; the statistical evidence suggests that both phenomena may have a common unknown cause.

Rheumatoid Arthritis.—Short, Abrams and Sartwell studied the clinical features of early rheumatoid arthritis in 293 unselected patients and a similar number of matched controls. Sixty-four per cent of the subjects were women, but men predominated among 39 patients with spinal involvement. The age of onset was compared with census figures for age distribution. There appeared to be no significant departure for men, but in women a decided increase was discovered in the age group of 50 to 54. Although this suggested an influence of the climacteric, special analysis revealed no close correlation between the cessation of menstruation and the onset of the disease. Personal or familial allergy did not occur in significantly greater frequency among the patients than among the controls. However, there was a significantly increased familial incidence of both rheumatoid arthritis and rheumatic fever in patients as compared with controls. In 70 per cent of 262 patients whose disease began in peripheral joints, symmetrical involvement was present from the onset. Large and small joints of the extremities were affected with equal frequency and those of the legs oftener than those of the upper extremities. In one sixth of the patients the onset was monarticular, eventually proceeding to polyarthritis. Fifty per cent of the patients who had spinal involvement on admission experienced the onset of

rheumatoid disease in peripheral joints, usually of the lower extremities. The appearance of articular symptoms and signs was most commonly preceded by a number of precipitating factors. Of these, strains, either mental or physical, and acute infections by far outranked in frequency exposure to cold or dampness, surgical operations, trauma or pregnancy.

A comprehensive investigation of "etiological factors" was undertaken by the Empire Rheumatism Council (1950*a*). The important negative finding was that most of the circumstances which have been presumed to bring about rheumatoid arthritis occurred as often in controls as in subjects. However, the study suggested a possible role of familial predisposition and an effect of cold and damp climate and of pregnancy and menopause. Also contrary to common concepts, the incidence of actual or potential foci of infection did not appear significant in 100 patients with rheumatoid arthritis studied by Davidson and his co-workers. Similarly, only about 10 per cent of 250 patients with ankylosing spondylitis reviewed by Simpson and Stevenson had a history or evidence of focal infection. The great variability in the onset of rheumatoid arthritis, ranging from barely perceptible and often extra-articular manifestations to fulminating febrile disease and its eventual transition into progressive symmetrical polysynovitis, deserves mention (Egelius and others; Short).

Rheumatic Fever.—Differentiation between rheumatoid arthritis and rheumatic fever in their typical forms rests on fairly well defined empirical concepts. Studies on the pathology of connective tissue diseases, cited earlier, have challenged the segregation of rheumatic fever and rheumatoid arthritis (Bauer and others; Rosenberg). It was demonstrated that the incidence of rheumatic heart disease among patients who have died with rheumatoid arthritis is far higher than in the general population. An attempt, therefore, was made to discover evidences of myocardial and endocardial disorders by clinical means in 114 patients with peripheral rheumatoid arthritis and 33 patients with spondylitis, compared with 100 nonarthritic persons. The incidence of rheumatic heart disease was not notably higher in the patients than in the controls (Rosenberg and others), suggesting that a significant portion of rheumatoid patients have subclinical cardiac disease. The difficulty of antemortem recognition of rheumatic heart disease was also expressed in the finding (Gardner and White) that an anatomically correct diagnosis was made in only seven of 32 patients who had combined coronary and rheumatic heart disease, and in 62 per cent of 50 patients with rheumatic heart disease proved at autopsy (Kaufman and Poliakoff). Only insignificant morbidity may be associated with cardiac sequelae of rheumatic fever (Bachman). Eighty-two of 47,000 soldiers between the ages of 17 and 34 were observed to have rheumatic valvulitis. Without symptoms of functional cardiac impairment, a past history of

rheumatic fever could readily be elicited. As might be expected of those patients who were not disabled despite having rheumatic valvulitis, only 48.5 per cent showed megalocardia.

Laboratory Tests.—The value of various laboratory procedures in the diagnosis of rheumatic diseases was further studied (Anderson and McCarty; Brainerd and Sokolow; Brown and others; deGara; Epstein and Gardam; Fischel; Fischel and Pauli; Fischel, Pauli and Lesh; Harris and Harris; Jawetz and Hook; Jowett; Kelley and others; Kissane and others; Nelson and Seal; Pokress and Goldberger; Poulsen; Quinn and Liao; Shapiro and others; Sulkin and others; Svartz and Schlossmann). These numerous investigations into the serologic, immunologic, roentgenographic and cardiographic reactions of patients with rheumatic disease have contributed to the understanding of the various disorders without furnishing absolutely conclusive diagnostic tools. Despite the lack of a specific laboratory method and although the separation between rheumatoid arthritis and rheumatic fever occasionally may be impossible even on histological grounds, the clinician need not be unduly concerned with departures from traditional diagnostic patterns, as they involve a relatively small number of borderline cases.

TREATMENT

Therapeutic Criteria.—The development of a standard of therapeutic efficacy in the treatment of rheumatic diseases has long been awaited. Critical evaluation of various agents and their comparison have ever suffered from the lack of a uniform measure. At the Seventh International Congress on Rheumatic Diseases, held in the summer of 1949, where the greatest single advance in experimental treatment of arthritis was reported, Steinbrocker, Traeger and Batterman announced the "Therapeutic Criteria in Rheumatoid Arthritis." This set of recommendations affords a gage of therapeutic results derived as much as possible from objective evidence. Study and use of this standard are recommended to all clinicians engaged in the appraisal of new forms of therapy in arthritis. At a time that investigative treatment in this field has become greatly intensified, this yardstick should prove valuable especially in the hands of those with clinical experience.

Clinical Effects of ACTH and Cortisone.—Shortly after Hench delivered, in London, the Heberden Oration on the "Potential Reversibility of Rheumatoid Arthritis" during the spring of 1949, Hench, Kendall, Slocumb and Polley (1949*a*), reported the effects of cortisone and of ACTH which had been observed since September 1948 on patients with rheumatoid arthritis. It was immediately evident that these hormones would control the clinical and laboratory manifestations of rheumatoid arthritis in a manner not hitherto achieved by any agent or measure. The impact of this discovery was all the greater because the

clinical application of these hormones could not have been readily anticipated from their known physiological properties. The validity and thoroughness of the initial observations may be gaged by the fact that after 1½ years of extensive clinical research with these hormones in rheumatoid arthritis few additions and no significant modifications have had to be made. The administration of cortisone or ACTH to patients with rheumatoid arthritis is followed within a few hours to two days by remarkable subjective relief of pain and stiffness and by progressive subsidence of the objective evidence of synovitis. Within a few days, the symptoms of systemic illness yield to a feeling of good health, even euphoria, and an increase in appetite and weight. Within 24 hours of the start of therapy, the characteristic guarding of movements disappears, indicating lessened pain and muscle spasm. The span of motion is increased, and even fibrous flexion contractures of several months' standing may be released to permit of passive motion through a greatly augmented range. Clark, Ropes and Bauer observed diminution of pain at rest, stiffness, pain on active motion, heat, effusion, tenderness and fatigability by about 80 to 90 per cent within four to six days of treatment. Severely ill and disabled patients may spontaneously undertake normal activities after 10 days of therapy.

The laboratory signs of rheumatoid arthritis improve more slowly. The sedimentation rate may remain elevated for several weeks before it returns to normal or near normal levels. The hematocrit usually rises promptly, and the synovial mucin tends toward normal quality and concentration. The beneficial effects of ACTH or cortisone on rheumatoid arthritis have been confirmed by a number of investigators (Boland, 1950 *a*; Boland and Headley; Brøchner-Mortensen and others; Clark and others; Freyberg, 1950 *a*; Markson; O'Connell and Burns; Ragan, Grokoest and Boots; Spies and others; Thorn and others, 1950) and were also observed in Still's disease (Stillman and Bayles), spondylitis (Boland, 1950 *a*; Freyberg, 1950 *a*) and arthritis associated with psoriasis (Boland, 1950 *a*).

Hench, Slocumb, Barnes, Smith, Polley and Kendall were the first to treat three adolescent patients suffering from acute rheumatic fever with cortisone and described rapid disappearance not only of fever, tachycardia and polyarthritis but also of elevated sedimentation rates and of abnormalities of the electrocardiogram. Hench, Kendall, Slocumb and Polley (1949 *b*) observed clinical effects of ACTH in rheumatic fever paralleling those obtained with cortisone, as did Massell, Warren and Sturgis. Compared with the course of that disease under ordinary therapeutic measures, these results appeared unusual in that in nearly all the patients the important manifestations of rheumatic fever promptly disappeared, namely, pyrexia, arthritis, subcutaneous nodules, signs of

valvular disease, pericarditis, congestive failure, paroxysmal tachycardia and elevation of the sedimentation rate (Massell, Warren, Sturgis, Hull and Craige).

In a number of other rheumatic syndromes variable results have been obtained with cortisone or ACTH (Baehr and Soffer; Bayles, Stout, Stillman and Lever; Boland, 1950 *b*; Elkinton and others; Goldman and others; Hertz and Forsham; Margolis and Caplan, 1950; Oppel and others; Plotz, Blunt and Ragan; Ragan; Robinson and others; Shick and others; Thorn and others, 1950; Wolfson and Cohn). While the diseases of connective tissue have been the principal subject of clinical trials by a number of patients treated, well over 50 clinical entities have been screened for their susceptibility to cortisone or ACTH. Despite the relatively large volume of work which has been reported or is in progress, the clinical usefulness of the hormones in chronic arthritis cannot be appraised, even tentatively, at this stage. It appears likewise imprudent to compare their effects in various diseases with which arthritis may be associated as a major or secondary manifestation. A reasonable assumption may be made that the hormones exert a generic influence on the inflammatory lesions of connective tissue diseases. It is more difficult to estimate whether the improvement in patients with a notably cyclic-disease like acute rheumatic fever promises greater practical benefit than do the transient and partial remissions seen in patients with periarteritis, disseminated lupus, dermatomyositis and scleroderma, respectively. Several years of clinical trial will be required before valid information of such nature becomes available.

Negative Results and Complications.—The production of both ACTH and cortisone is now adequate to cover the demand for clinical investigation, under the restriction of Section 505 of the Federal Food, Drug and Cosmetic Act. With increasing supply and demonstrated usefulness in certain nonrheumatic conditions, one may expect more extensive application of these hormones in medical practice, but one must hope for full realization of their limitations and formidable risks. The original communications (Hench, Kendall, Slocumb and Polley, 1949 *a*; Hench, Slocumb, Barnes, Smith, Polley and Kendall, 1949) described the rapid recurrence of rheumatic disease activity on withdrawal of hormone therapy, an observation substantiated in about 85 per cent of patients with rheumatoid arthritis, as well as in those with other diseases so treated. These flares have generally been as severe at the pretreatment condition. In few instances, probably no more than may be expected in chronic remitting diseases, continued defervescence of the rheumatic state for well over one year has been observed. Protracted administration of either hormone rapidly brought into focus certain so-called toxic effects. In rare cases, especially with ACTH administration, drug sensitivity characterized by fever and dermatitis was noted

(Proceedings of the First Clinical ACTH Conference; Stillman and Bayles). This has not prevented further therapy after desensitization or changing to another product. Earlier preparations of ACTH contained admixtures of other anterior, and some posterior, pituitary hormones. Evidence of vasoconstriction and abdominal cramps, however, has become rare since purified extracts have been available. Epileptiform convulsions and psychiatric disturbances requiring confinement and manifested by disorientation, mania or profound depression have followed the extended use of either drug in patients with widespread vascular disease and with uncomplicated rheumatoid arthritis (Hoefer and Glaser). The mechanism and prevention of this complication are obscure, but the clinician may find it advantageous to undertake a careful psychiatric evaluation before institution of treatment and to inform the patient's family of this particular hazard. These disturbances have in most cases disappeared after cessation of therapy.

Many patients treated with antirheumatic doses of ACTH or cortisone show a rise in the fasting blood sugar level and glycosuria. This complication likewise disappears when therapy is discontinued. If diabetes mellitus develops, it probably represents the precipitation of a latent disorder. Preexistent diabetes is accentuated by use of ACTH or cortisone. Minimum safeguards in this respect consist of appraising the patient's personal and family background, an initial dextrose tolerance test and regular qualitative urinalyses. Diabetes mellitus is a contraindication to chronic therapy, but short term treatment for critical conditions may be given if sufficient insulin can be administered to maintain control of diabetes. Like the disturbances in carbohydrate metabolism, the changes in electrolyte balance encountered with protracted administration of ACTH or cortisone in antirheumatic doses frequently produce undesirable, even serious, reactions. They represent extensions of the physiological properties of these agents. Hypochloremic, hypokalemic alkalosis may occur with or without significant laboratory evidence of sodium and water retention. Potassium deficiency is characterized clinically by weakness and paralysis of skeletal muscles and intestinal distention. This disturbance may be recognized by the results of serum potassium determinations, which should be made at regular intervals during chronic administration of ACTH or cortisone. Cardiographic changes may be helpful but are not specific in potassium deficiency. Abnormally low potassium concentrations are associated with a prolongation of the Q-T interval, lowering or inversion of the T waves, ectopic systoles and auriculoventricular block. It is essential to weigh the patient regularly for the early recognition of edema. If the plasma carbon dioxide–combining power exceeds 70 volumes per 100 cc., mild akalosis is present. The disturbances in electrolyte balance may be minimized or obviated by restriction of dietary sodium to

less than 0.6 Gm. per day and the simultaneous administration of enteric-coated* capsules of potassium chloride, 0.3 Gm., five to 10 daily. Retention of sodium chloride and water occurs more frequently in patients treated with ACTH than in those treated with cortisone; in fact, the latter may enhance excretion of water by interference with tubular resorption (Gaunt and others). The use of mercurial diuretics in ACTH-induced edema will increase the renal loss of potassium.

The blood pressure should be determined at regular intervals, although hypertension has been an infrequent complication of therapy. In preexistent hypertension the use of ACTH is contraindicated. In nearly all patients receiving cortisone or ACTH for several weeks or longer, one or more features of the hyperadrenal habitus, such as florid, round facies and massing of subcutaneous tissue in the cervical and supraclavicular regions, hirsutism and increased pigmentation, will develop. These constitute a cosmetic annoyance rather than a serious complication and will revert, as a rule, after therapy. The tendency to increased breakdown of protein may be balanced by simultaneous administration of testosterone and, to some extent probably, by replacement of potassium. Decrease or depression of menses occurs frequently with administration of either hormone and lasts until the inhibition of pituitary gonadotropin is removed. Although it is desirable to begin treatment in hospital patients, the minimal safeguards outlined above will permit of ambulatory therapy. A number of modifications are now under scrutiny (Astwood and others; Edström; Markson). The ACTH extract prepared by Astwood and his co-workers has enhanced physiological potency. Peptide fractions of the pituitary hormone afford a purified agent and economy of raw materials. Oral administration of cortisone, if effective, will reduce the cost of manufacture and facilitate administration. These developments, as related to the treatment of rheumatic diseases in general, are of purely technical significance. They do not remove the limitations and risks described earlier. Interval administration of the hormones so far has not proved satisfactory.

Presumptive Indications.—Pending a complete appraisal of their usefulness, cortisone or ACTH may reasonably be given today in certain critical phases and in grave complications of rheumatic diseases. Fulminating rheumatic fever with severe pancarditis became apparently inactivated and remained so for the observational period of eight to 10 months after the use of cortisone in doses of 200 mg. for the first few days, followed by 100 mg. daily to a total of 3.5 to 5 Gm. given in 22 to 40 days. Similar results were obtained with ACTH in doses of 25 to 60 mg. for three to four days, followed by 10 to 15 mg. daily for a total of 500 to 800 mg. over two to five weeks (Hench, Kendall, Slocumb and Polley, 1950; Massell, Warren, Sturgis, Hull and Craige). Iritis and episcleritis are serious complications of rheumatoid disease

and may profoundly affect the prognosis for rehabilitation. Mann and Markson reported the prompt and lasting subsidence of such lesions in the chronic progressive form after ACTH was given daily for 29 days in doses of 30 mg. gradually reduced to 10 mg. Talkov, Colpoys, Davis, Papper and Feinberg observed disappearance of some and regression of all scleral nodules in one patient during treatment with cortisone. Massive pericardial effusion, threatening tamponade, one of the rare fatal complications of rheumatoid arthritis, would also be a presumptive indication for treatment with these hormones. If acute gouty arthritis cannot be controlled by adequate amounts of colchicine and salicylates within 72 hours, ACTH in doses of 50 mg. in single or 80 mg. in divided injections for the first day, and in decreasing quantities for the next two to three days, may be administered. Prompt alleviation of all symptoms and signs has been reported by several investigators (Bishop and others; Boland, 1950 *a*; Robinson and others; Thorn and others, 1950; Wolfson and Cohn). In most patients so treated, gouty arthritis will recur after withdrawal of ACTH, but according to Wolfson and Cohn, the recrudescence can be prevented by administration of colchicine either simultaneously with or after that of ACTH. It cannot be said with certainty whether cortisone has a comparable effect on gouty arthritis. The success of ACTH as a provocative agent in gout was described by Hellman.

Investigational Treatment.—While ACTH and cortisone therapy reportedly has benefited some patients moribund with disseminated lupus and other collagen diseases, it failed in other instances to alter the natural course, although the preparations were given in large doses over a period of several weeks. In the general field of rheumatic disease, use of these hormones must be considered, as yet, a form of experimental therapy. In a few patients with severe rheumatoid arthritis and in several patients with the moderate and mildly active form the disease has been more or less controlled with so-called maintenance doses of cortisone ranging from 25 to 55 mg. daily, or 100 mg. three times weekly (Boland, 1950 *a*; Freyberg, 1950 *a*; Hench and others, 1950) or with administration of 10 to 15 mg. twice daily of ACTH (Markson; Ragan; Grokoest and Boots). The choice between ACTH and cortisone as therapeutic agents in rheumatic diseases still is subject to investigation. While these preparations differ greatly in physical and chemical properties, as well as in their range of targets and physiological effects, the antirheumatic action of either appears to be mediated through the adrenal cortex and may be dependent on the secretion of 17-hydroxycorticosterone (Kendall's compound F). For experimental purposes it is well to realize that 5 to 10 mg. of ACTH constitutes a minimal physiological dose, effective in man for 30 minutes to six hours after intramuscular injection (Thorn and others, 1950).

A dose as large as 200 mg. given intravenously to a normal volunteer caused no significant toxicity except for a mild pyrogenic reaction (Sayers and others). The physiological activity of cortisone in doses of 50 to 200 mg., measured by the eosinopenic response and by increase in 17-ketosteroid excretion, appears to be less than that of ACTH in doses of 40 to 100 mg. Prolonged administration of cortisone, moreover, is known to produce functional and even structural atrophy of the adrenal cortex (Antopol), rendering it insusceptible to stimulation for about one week after cortisone therapy has been discontinued. With both cortisone and ACTH endogenous corticotropins are suppressed, but the adrenopause following use of ACTH is shorter by several days and less pronounced than that after administration of cortisone (Thorn and others, 1950). Relatively larger initial amounts of cortisone, such as 100 to 200 mg. daily, appear to be more effective than an ascending dosage schedule. In children, active rheumatoid arthritis has been controlled with administration of 20 mg. of ACTH in divided doses and rheumatic fever with 0.5 to 1 mg. per kilogram of body weight, but in a patient of comparable development and disease activity, treatment with 50 mg. of cortisone may be ineffective.

A number of other steroids extracted from the adrenal cortex and the gonads or synthesized from plant and animal sources, given either singly or in combination with other steroids and with vitamin C, have been tested for their physiological properties and, clinically, for their antirheumatic effect (Alexander and Duthie; Bywaters and others; Currie and Will; Douthwaite; Empire Rheumatism Council, 1950 *b*; Fletcher and others; Fox; Freemen and others; Hart and Starer; Ishmael and others; Kellgren; Kersley and others; Kyle and Crain; LeVay and Loxton; Lewin and Wassén; Loxton and LeVay; Newman; Reich; Spies and others; Terry and London). The results are sufficiently divergent to render appraisal difficult, but none of these agents or measures has achieved the standard of uniform and predictable action set by cortisone or ACTH. It was inevitable and necessary for many compounds on the recently enlarged horizon of antirheumatic therapeutics to be tested on grounds of theoretical expectancy or merely for systematic screening (Massell, Warren, Patterson and Lehmus; Seifter, Baeder, Begany and others; Spies and Stone, 1949; Hartfall and Harris). Much valuable physiological and clinical information may be gained from this work. Unfortunately, however, the results of incomplete investigations have occasionally been misused or misconstrued in the promotion of drugs.

General Treatment.—While new methods of therapy are in the stage of study and development, the practicing physician will do well to rely on established means of treating rheumatic diseases. It is pertinent to recall that by such measures over 75 per cent of all patients with rheu-

matic disease within the experience of the average physician may be adequately treated. Among those remedies salicylates rank foremost, and several investigations have shed further light on their action and optimal uses (Hoffman and others; Reid and others; Talkov, Ropes and Bauer; Watkinson). Sodium gentisate has been found as effective as salicylates in the treatment of rheumatic fever without inducing the same toxic reactions (Medical Practices Committee for England and Wales). On the other hand, succinates and the addition of heparin to salicylates did not appear to have any value in the treatment of rheumatic fever or rheumatic carditis (Glazebrook and Wrigley). Although in this past year the opportunity for pharmacologic and clinical studies on chrysotherapy in rheumatoid arthritis was obviously lessened, the indications for the use of gold salts continue (Adams and Cecil; Archer; Forestier; Freyberg, 1950 *b*; Losada and France), as the rate of remissions obtained with them is about twice as high as those occurring in a comparable series of control patients treated by supportive methods alone. Aurothioglycolanilide did not exert palliative or suppressive effects on rheumatoid arthritis (Friedman and Steinbrocker). Two instances of purpura due to gold therapy were described, one of which was fatal (Kroese). Sporadic reports on roentgen therapy in various forms of rheumatism were concerned with short term clinical observation, mainly on symptomatic manifestations, such as pain and muscle spasm (Hilton; King; Query). Roentgen therapy has been conceded a modicum of palliative benefit in ankylosing spondylitis (Mallender). Its usefulness, especially in osteoarthritis, may be out of proportion to the risks of high voltage roentgen exposure.

To the nonspecific supportive effect of blood transfusions in rheumatoid arthritis (Simpson and others) has recently been added a specific indication for postpartum plasma which is claimed to result in a higher rate of remissions (Granirer; Moore and others); not widely substantiated in its results, the report invites study on the presence of adrenergic principles in postpartum blood. Spasmolytic and analgesic agents, including procaine given intravenously and tetraethyl ammonium bromide (Fløystrup, Graubard and Peterson; Howell; Lagen; Margolis and Caplan, 1949; Norcross and others), may become adjuncts to an integrated system of physical therapy for various forms of rheumatism. The value of such a program is not sufficiently appreciated, and measures capable of prevention and treatment of deformities need to be more widely known and used (Engel and others; Hamilton; Collins and Gibson; Hollander and Horvath; Horvath and Hollander; Martin and Erickson; Tegner; Turney; Wakim and others). Hill and Holbrook have presented their experiences with this important phase of rheumatism in articles and exhibits which permit of ready application to the problems of medical practice.

CONCLUSIONS

Whether the studies of recent months considered here have brought us closer to the control and prevention of rheumatic diseases remains for a future report to tell. Today, one can count three notable developments. First, physiological thinking has largely replaced the rigid descriptive approach to rheumatology and has fostered the definition of several rheumatic diseases in terms of a systemic lesion. This concept of connective tissue disorders goes far to reconcile the balance between various syndromes. Second, the past year has witnessed the participation in rheumatological research, on a large scale, of physicians and scientists from other clinical and fundamental disciplines. The gain of additional workers, experienced in the use of methods newly applied to this field, has increased the rate and spread of research. Last, and uppermost in importance, several chronic rheumatic diseases which heretofore could be studied only in their natural course and in unsatisfactory animal analogs may now be observed in an experimental situation.

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Book Reviews

Thyroid Hormones and Their Action. By G. Mansfield. Pp. 157, with 57 diagrams. Frederick Muller Ltd., 29 Great James St., Bedford Row, London, 1950.

This absorbing little book is the chronicle of a lifetime spent in research on thyroid physiology. The author has devoted a great deal of his research to various fundamental aspects of thyroid physiology. The first portion of the book is given to a study of experimental macrocytic anemia produced by various means in which the author demonstrates that in thyroidectomized animals it is necessary to give a thyroid fraction in addition to liver extract to produce remission. The thyroid fraction which is necessary is distinct from thyroxin, and the author terms this the "myelotropic" hormone.

With regard to thyroxin, the author cites an interesting series of experiments to prove that it reaches the peripheral organs by means of the peripheral nerves. It then exerts its typical known action on the end organs.

The last half of the book is devoted to the story of the isolation in crystalline form of two additional thyroid hormones, thermothyrin A and B. These substances are released from the thyroid gland under the stimulus of heat or cold, and both of them have the property of diminishing oxygen consumption in the intact animal. However, in the thyroidectomized animal the opposite effect is apparent. The author concludes with the extremely interesting speculation that toxic diffuse goiter is a disease in which thyroxin secretion is deficient, the effects of which are apparent in the so-called myxedema-like symptoms. In addition, he states that the toxic symptoms in the patient are due to the secretion of large amounts of thermothyrin in the absence of thyroxin. This theory is further substantiated by the finding of thermothyrin in the serum of patients with toxic diffuse goiter but not in normal subjects.

Brucellosis: Clinical and Subclinical. By Harold J. Harris, M.D., F.A.C.P. Second edition. Price, $10. Pp. 617, with 44 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1950.

One can have nothing but praise for this handsome monograph. The writer, a student of Brucellosis for many years, brings up to date in the second edition of his book about all there is to know of brucella infections. No phase of the subject has been slighted, as evidenced by the bibliography of over seven hundred references; that the information is complete is shown by full discussion of the recently introduced antibiotics, aureomycin and chloramphenicol. The volume is made in Hoeber's best style; handsome format, fine paper, good print and beautiful illustrations.

Physical Studies of Action of Sodium Fluoride on Human Enamel. By D. B. Scott, Ph.D., R. G. Picard, Ph.D., and R. W. G. Wycoff, Ph.D. Public Health Reports 65, 43, 1950.

This study is an attempt to obtain further information concerning the mechanism of action of the fluoride ion in the control of dental caries. Polished surfaces of enamel treated with sodium fluoride solutions for periods varying from five minutes to thirty days and samples prepared by etching with acid before and after exposure to sodium fluoride were studied with the electron microscope. Another phase

involved electron diffraction studies of the crystalline composition of the surfaces of enamel slabs before and after similar treatment.

Few visible surface changes were noted when the treatment with sodium fluoride was given less than seven days. Small amounts of surface deposits were seen after seven days and greater amounts after a fifteen and a thirty day exposure. The deposit was removed by prolonged washing with distilled water. The result of the relative acid solubilities of enamel untreated and treated with sodium fluoride was inconclusive and preliminary in nature. Electron diffraction patterns made of the enamel surface before and after contact with sodium fluoride showed a change from the original apatite pattern to that of calcium fluoride.

JOSEPH C. CALANDRA.

Menstruation and Its Disorders. By Earl T. Engle, M.D. Price, $6.50. Pp. 338. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

According to the cover jacket and advertisements of the publishers, this book is "certain to become the outstanding desk-reference-work on this subject for gynecologists, endocrinologists, urologists, pathologists, and surgeons and will be helpful to many practicing physicians, medical students, welfare directors and general readers." This is not true. The book is an excellent symposium on various basic subjects, most, but not all, of which are related directly or indirectly to the phenomena of menstruation. The thirteen chapters are contributed by men who are authorities in their special fields. Only three of the sections have to do with subjects that have clinical application. The book will be of interest and of value to those clinicians and research workers who are particularly interested in the cause and mechanism of both normal and abnormal menstruation. It will not be of interest or of value to the general physician, much less to the medical student, welfare director or general reader.

Fundamental Considerations in Anesthesia. By Charles L. Burstein, M.D. Price, $4. Pp. 153, with 64 illustrations. New York: The Macmillan Company, 1949.

This excellent little book does not deal at all with the actual technic of putting patients to sleep and of smoothly controlling anesthesia. It deals rather, as the name would imply, with the physiology of the circulation and of respiration, especially from the standpoint of those disturbances which may occur under anesthesia. An example is the discussion of how and why a patient whose respiratory center is depressed may stop breathing altogether if he is given inhalations of oxygen. The material is clearly and simply presented and should be useful, not only to anesthesiologists, but to physicians in general.

Evaluation of Chemotherapeutic Agents. By Colin M. MacLeod, M.D. Price, 4. Pp. 205. New York: Columbia University Press, 1949.

This is a report of a symposium of the Section on Microbiology of the New York Academy of Medicine. The contributors are outstanding ones in the field of the study of chemotherapeutic agents. Fourteen subjects are discussed, each representing addresses presented on March 25 and 26, 1948. Among the subjects discussed are the relation of blood concentration to the therapeutic effects of the chemotherapeutic agents, renal excretion of the agents, distribution and protein binding of the chemicals, chemoprophylaxis, antimalarial drugs, chemotherapy in

viral infections and chemotherapeutic agents in cancer. This excellent book should be of value to clinicians, medical students and investigators in the field of infectious diseases.

Atlas of Tumor Pathology. Prepared at the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council.

Tumors of the Peripheral Nervous System (Section II—Fascicle 6). By Arthur Purdy Stout, M.D., professor of surgery, Columbia University, College of Physicians and Surgeons, New York. Pp. 57, with 56 illustrations. Price $0.60. American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C., 1949.

This fascicle on tumors of the peripheral nervous system is the first of 39 to be published concerning tumors of various organs. With it is provided an introduction and an index for the entire series to follow. This ambitious index, jointly sponsored and supported by six organizations, will have over 30 authors. The stated purposes of the atlas include attempts to standardize and simplify nomenclature of tumors and to aid teaching of oncology. The atlas will illustrate the usual patterns of tumors of each organ and their variants, and give in text the outstanding characteristics of each. The fascicles are printed in loose-leaf form to facilitate binding in correct sequence and aid in inserting improvements. Subsequent fascicles will be briefly reviewed as they are published.

The present fasicle, or chapter, written by Dr. Stout, is an auspicious debut for the atlas. Few subjects in the classification of tumors could have been chosen which are more controversial than this. The first objective of the atlas, namely, the standardization of nomenclature, is thus at once put to a severe test. If unanimity of acceptance is not achieved it will not be due to lack of scholarship and forthrightness of the author but to the complexity of the problems, the scarcity of definitive scientific answers and the lack of adequate space.

Atlases must be brief. Where noncontroversial objective matter is presented, as, for example, in geographic maps, this is no handicap but an asset. In presenting controversial and subjective material, however, brevity may be a serious handicap, as is shown by the present instance. The author divides the common tumors of peripheral nerves into two main groups, neurilemmomas and neurofibromas. He does not use enough space, pictorial or textual, to present the data to justify this classification convincingly. No essential difference is evident between figures 12 and 25, although in the text and in other illustrations points of difference between the two types are made. The author's previous publications have given more evidence.

This defect inherent in the atlas method shows why longer books cannot be dispensed with for presenting subjects which are in a state of flux. Despite disagreements, it would be desirable if authors writing on this subject in the future would adhere to the present nomenclature unless they give good evidence for not so doing. As it stands the fascicle is a beautifully illustrated, brief but clearly written description of these tumors. It sets a high standard for authors of other fascicles which, if it is achieved, assures a hearty reception for the entire atlas.

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VOLUME 86
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CONTENTS OF VOLUME 86

JULY 1950. NUMBER 1

PAGE

Cardiac Disease and Rheumatoid Arthritis. James Y. Bradfield, M.D., and Milton R. Hejtmancik, M.D., Galveston, Texas 1

Clubbing of Digits, Metaplasia of Urinary Bladder and Mucous Diarrhea. Thomas A. Warthin, M.D.; John F. Cooper, M.D., and Anthony P. Caputi, M.D., West Roxbury, Mass. 10

Hemolytic Anemia with Paroxysmal Methemoglobinemia and Sulfhemoglobinemia: Report of Two Cases. Alfred S. Evans, M.D., New Haven, Conn.; Norbert Enzer, M.D., Milwaukee; Howard A. Eder, M.D., New York, and Clement A. Finch, M.D., Boston 22

Pseudocystic Disease of Bone. W. E. Jacobson, M.D., Minneapolis 35

Extensive Laboratory Studies of a Patient with Pheochromocytoma Before and After Successful Operation, with a Note on the Trial of Piperidylmethyl Benzodioxane to Differentiate Such Conditions from Essential Hypertensive Vascular Disease. Robert W. Wilkins, M.D.; William E. R. Greer, M.D.; James W. Culbertson, M.D.; Meyer H. Halperin, M.D.; Julius Litter, M.D.; Charles H. Burnett, M.D., and Reginald H. Smithwick, M.D., Boston 51

Alkaptonuria, Ochronosis, Arthritis and Ruptured Intervertebral Disk Complicated by Homologous Serum Reaction. Harry Eisenberg, M.D., Butler, Pa. 79

Progress in Internal Medicine:

Cardiovascular Diseases: Review of Significant Publications, July 1947 to June 1949. Royal S. Schaaf, M.D., with the Editorial Assistance of Edward F. Bland, M.D., Boston 87

News and Comment 161

Book Reviews 162

AUGUST 1950. NUMBER 2

Letter from the Editorial Board 167

Diagnostic Problems in Jaundice. Franklin M. Hanger, M.D., New York ... 169

Time Action of Globin Insulin Compared with That of Protamine Insulin Modifications. Arthur R. Colwell, M.D.; Joseph H. Rohr, M.D., and Blanchard B. Reeb, M.D., Chicago 178

Effect of Feeding Egg Yolk and Cholesterol on Serum Cholesterol Levels. William J. Messinger, M.D.; Yetta Porosowska, M.S., and J. Murray Steele, M.D., New York 189

Intraventricular Block: Review of the Literature. R. H. Rosenman, M.D.; A. Pick, M.D., and L. N. Katz, M.D., Chicago 196

Primary Hodgkin's Disease of the Lung. Krikor Yardumian, M.D., and Leonard Myers, M.D., Pittsburgh 233

Primary Atypical Amyloidosis: Report of a Case. W. Noel Whittlesey, M.D., New York 245

Hiatus Hernia: Analysis of Twenty-Five Cases. Eugene E. Simmons, M.D.; Robert S. Lang, M.D.; Howard B. Hunt, M.D., and Ralph C. Moore, M.D., Omaha 253

AUGUST—*Continued*

PAGE

Changing Pathogenesis of Addison's Disease, with Special Reference to Amyloidosis. Ward M. O'Donnell, M.D., Ann Arbor, Mich..... 266

Lipophagic Intestinal Granulomatosis (Whipple's Disease): Clinical and Pathologic Study of Thirty-Four Cases, with Special Reference to Clinical Diagnosis and Pathogenesis. Kemp Plummer, M.D.; Simon Russi, M.D.; William H. Harris Jr., M.D., and Charles M. Caravati, M.D., Richmond, Va. 280

News and Comment..... 311

Book Reviews 312

SEPTEMBER 1950. NUMBER 3

Clinical Studies with ACTH and Cortisone in Renal Disease. George W. Thorn, M.D.; John P. Merrill, M.D.; Stephen Smith III, M.D.; Marcel Roche, M.D., and Thomas F. Frawley, M.D., Boston..... 319

Nitrogen Shift in Cancer. Jeanne C. Bateman, M.D., Washington, D. C.... 355

Sudden and Unexpected Natural Death: V. Causes of Death Classified by Sex and Age. S. M. Rabson, M.D., Fort Wayne, Ind..... 361

Hepatic Insufficiency and Cirrhosis in Diabetes Mellitus. Joseph J. Frankel, M.D.; Clyde E. Asbury Jr., M.D., and Lyle A. Baker, M.D., Hines, Ill... 376

Infectious Mononucleosis with Hepatitis. Hugh D. Bennett, M.D.; Joseph J. Frankel, M.D.; Paul Bedinger, M.D., and Lyle A. Baker, M.D., Hines, Ill.. 391

Extramedullary Plasmacytoma Involving Pharynx, Skin and Lymph Nodes. Paul Kent Switzer, M.D., Union, S. C.; Vince Moseley, M.D., and William Maurice Cannon, M.D., Charleston, S. C..... 402

Cardiopathy in Friedreich's Ataxia (Spinal Form of Hereditary Sclerosis): Review of Literature and Analysis of Cases of Five Siblings. Thomas H. Lorenz, M.D.; Chester M. Kurtz, M.D., and Herman H. Shapiro, M.D., Madison, Wis..... 412

Recent Progress in Insulin Physiology. Ernest Bruch, Ph.D., M.D., Rockford, Ill. 427

Progress in Internal Medicine:

Gastroenterology: A Partial Review of the Literature from July 1948 to July 1949 (To Be Concluded). Joseph B. Kirsner, M.D.; Walter Lincoln Palmer, M.D.; William E. Ricketts, M.D.; Julian W. Buser, M.D., and Homer C. Marshall, M.D., Chicago..... 443

News and Comment..... 487

Book Reviews..... 488

OCTOBER 1950. NUMBER 4

Clinically the Myocardium. Henry A. Christian, M.D., Brookline, Mass..... 491

Aureomycin in Prevention of Bacteremia Following Tooth Extraction. Oscar Roth, M.D.; A. L. Cavallaro, D.A.B.O.S.; Robert H. Parrott, M.D., and Rose Celentano, M. T. (ASCP), New Haven, Conn..... 498

Effects of Intravenous Injection of Typhoid Vaccine on Blood Leukocytes and Adrenal Cortex. M. D. Altschule, M.D.; Barbara H. Parkhurst, B.S., and Elaine Promisel, Boston..... 505

OCTOBER—*Continued*

PAGE

Serum Esterified Fatty Acids with Fat Tolerance Tests in Diabetes Mellitus. Edwin F. Hirsch, M.D., and Lynn Carbonaro, B.S., Chicago..... 519

Adult Renal Osteitis Fibrosa with Metastatic Calcification and Hyperplasia of One Parathyroid Gland: Report of a Case. E. Arthur Dreskin, M.D., Greenville, S. C., and Theodore A. Fox, M.D., Chicago..... 533

Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus. Louis J. Soffer, M.D.; Marvin F. Levitt, M.D., and George Baehr, M.D., New York..... 558

Case Reports:

Polyneuritis: Complete Pharyngeal and Respiratory Paralysis with Recovery. L. Richard Webb Jr., M.D., Springfield, Mo..... 574

Chronic Recurrent Nonhemolytic Streptococcic Endocarditis: Report of a Patient Treated Concurrently with Penicillin and Dihydrostreptomycin. William C. Robbins, M.D., and Ralph Tompsett, M.D., New York..... 578

Bacillus Subtilis Meningitis and Bacteremia: Report of a Case and Review of the Literature on "Subtilis" Infections in Man. Louis Weinstein, M.D., and Charles G. Colburn, M.D., Brookline, Mass.... 585

Progress in Internal Medicine:

Gastroenterology: A Review of the Literature from July 1948 to July 1949 (Concluded). Joseph B. Kirsner, M.D.; Walter Lincoln Palmer, M.D.; William E. Ricketts, M.D.; Julian W. Buser, M.D., and Homer C. Marshall, M.D., Chicago..... 595

News and Comment..... 641

Book Reviews..... 642

NOVEMBER 1950. NUMBER 5

Effects of Terramycin on the Bacterial Flora of the Bowel in Man. Joseph M. Di Caprio, M.D., and Lowell A. Rantz, M.D., San Francisco..... 649

Clinical, Functional and Needle Biopsy Study of the Liver in Alcoholism. Marvin Seife, M.D.; Bruce J. Kessler, M.D., and James R. Lisa, M.D., with the Technical Assistance of Frank Scudero, B.S. (Chem.), and Alida J. Ruiz, A.B., New York..... 658

Use of Choline Supplements in Fatty Metamorphosis of the Liver: A Needle Biopsy Investigation in Human Beings. Bruce J. Kessler, M.D.; Marvin Seife, M.D., and James R. Lisa, M.D., with the Technical Assistance of Frank Scudero, B.S. (Chem.), and Alida J. Ruiz, A.B., New York..... 671

Riehl's Melanosis and the Adrenal Glands. Leo Spira, M.D., Ph.D., London, England..... 682

Hematology of Atomic Bomb Casualties. George V. LeRoy, M.D., Chicago.. 691

Case Reports:

Hemolytic Anemia Secondary to a Familial (Hereditary) Defect in Hemoglobin Synthesis: Report of a Case with Radioiron Studies. Harold Mills, M.D.; Rex L. Huff, M.D.; Marcus A. Krupp, M.D., and Joseph F. Garcia, M.A., San Francisco..... 711

Insulin Resistance: Review of the Literature and Report of a Case Associated with Carcinoma of the Pancreas. John K. Davidson, M.D., and E. E. Eddleman, M.D., Atlanta, Ga..... 727

Progress in Internal Medicine:

Liver and Biliary Tract: A Survey of Tests for Hepatic Function; the Use of the Hepatic Star in the Differential Diagnosis of Jaundice. Carl H. Greene, M.D., Brooklyn..... 743

News and Comment..... 789

Book Reviews..... 790

DECEMBER 1950. NUMBER 6

PAGE

The Erythrocyte Coproporphyrin: Variation in Respect to Erythrocyte Protoporphyrin and Reticulocytes in Certain of the Anemias. C. J. Watson, M.D., with the Technical Assistance of Miss V. E. Hawkinson, Miss Irene Bossenmaier and Mrs. Rita Hughes, Minneapolis 797

Prophylaxis of Motion Sickness: Evaluation of Some Drugs in Seasickness. Major Herman I. Chinn, Medical Service Corps, United States Air Force; Werner K. Noell, M.D., Randolph Field, Texas, and Lieutenant Colonel Paul K. Smith, United States Air Force 810

Pheochromocytoma and Essential Hypertensive Vascular Disease. Marcel Goldenberg, M.D.; Henry Aranow Jr., M.D.; Alfred A. Smith, M.S., and Mogens Faber, M.D., New York 823

Current Concepts of Malaria, with a Review of Five Hundred and Ten Admissions to a Veterans Hospital. Robert Schwartz, M.D.; Matthew M. Mansuy, M.D., and Winfield C. John, M.D., Aspinwall, Pa. 837

Alterations in Renal Function, Including Hematuria, in Man During Intracranial Air Studies: Alterations in Cardiac Function. S. J. Weinberg, M.D.; J. R. Goodman, Ph.D., and M. C. Bushard, M.D., Los Angeles 857

Studies of Immunologic Reactions of Patients with Hodgkin's Disease: Antibody Reaction to Typhoid Immunization. George T. Hoffmann, M.D., and Antonio Rottino, M.D., New York 872

Gangrene of the Extremities: A Recently Recognized Complication of Severe Meningococcic Infection. H. A. Weiner, M.D., Staten Island, N. Y. 877

Progress Notes on Fifty Diabetic Patients Followed Twenty-Five or More Years. Ruth E. Reuting, M.D., Boston 891

Action of Atropine on the Cardiovascular System in Normal Persons. L. A. Nalefski, M.D., and C. F. G. Brown, M.D., Chicago 898

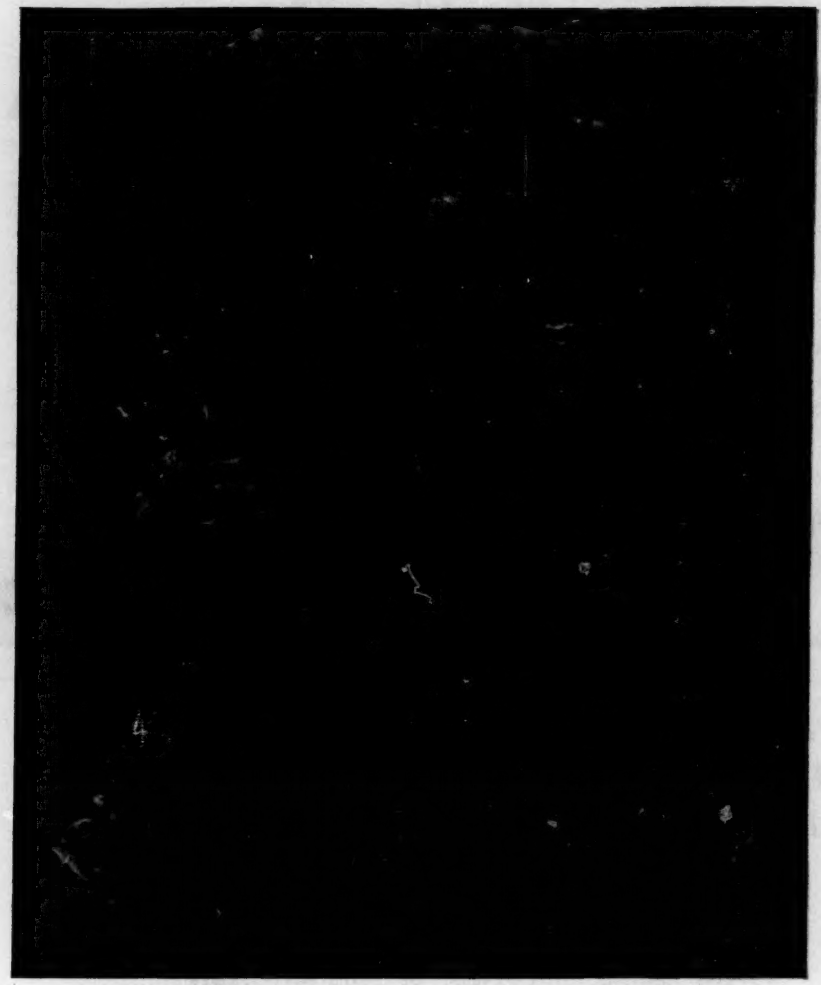
Liver Dysfunction Following Abdominal Operations: The Significance of Postoperative Hyperbilirubinemia. William Geller, M.D., and Henry J. Tagnon, M.D., New York 908

Studies on the Effects of Parenteral Quinidine Administration. Harris Blinder, M.D.; Julius Burstein, M.D.; William Horowitz, M.D.; Eugene Gersh, M.D., and Raanan Smelin, M.D., New York 917

Progress in Internal Medicine:

Annual Review of Rheumatic Diseases. Hans Waine, M.D., Boston 934

Book Reviews 970



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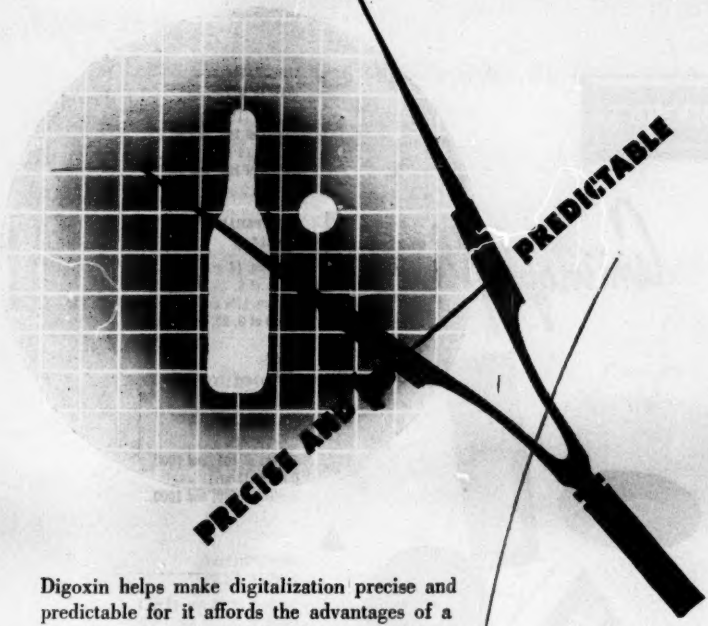

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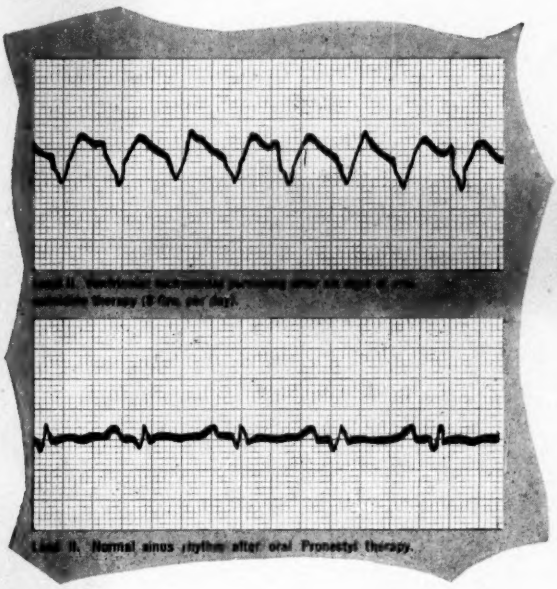

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Minnesota[5]	5000	535	10.7
Illinois[6]	4478	601	13.4
Oklahoma[7]	924	92	10.0
Washington[8]	1526	164	10.7
California[9]	1341	92	6.9
Louisiana[10]	4270	355	8.3
Tennessee[11]	20,237	2,305	11.4
New Mexico[12]	1284	190	14.8
Total	40,470	4,411	10.9

Intestinal. Comparative in vitro studies have shown that Milibis, the new intestinal amebacide, is one of the most powerful of the drugs commonly used against Endamoeba histolytica. In clinical tests Milibis has given excellent results in thousands of cases. In 82.6 per cent of those that could be followed parasitologically for prolonged periods, negative stools were obtained consistently after one to four courses of Milibis treatment.[13] There were virtually no side effects.

Dose for adults: 0.5 Gm. three times daily for seven days. If stools remain positive, course should be repeated. Supplied in tablets of 0.25 Gm., bottles of 50.

MILIBIS®
Bismuth Glycolylarsanilate

Extra-Intestinal. Aralen, an established antimalarial of relatively low toxicity, has been found remarkably effective in the treatment of extra-intestinal amebiasis (amebic hepatitis).[14-21] This discovery is particularly important because of the likelihood of extra-intestinal involvement in chronic amebiasis.

Dose for adults: 4 tablets daily in divided doses for two days, followed by 2 tablets daily for two to three weeks. Administer before, after or together with Milibis treatment. Supplied in tablets of 0.25 Gm., bottles of 100 and 1000.

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